In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. 17-1362V
Filed: November 27, 2023

ANDREW KALTENMARK and DANIELLE KALTENMARK, parents of A.J.K., a minor,

Petitioners,

v.

SECRETARY OF HEALTH AND HUMAN SERVICES,

Respondent.

Special Master Horner

Edward Kraus, Kraus Law Group, LLC, Chicago, IL, for petitioner.
Colleen Hartley, U.S. Department of Justice, Washington, DC, for respondent.

DECISION[1]

On September 28, 2017, A.J.K., a minor, by her father, Andrew Kaltenmark, filed a petition under the National Childhood Vaccine Injury Act, 42 U.S.C. § 300aa-10-34 (2012).[2] (ECF No. 1.) On December 5, 2017, the case caption was amended to "Andrew Kaltenmark and Danielle Kaltenmark, parents of A.J.K., a minor" ("Petitioners"). (ECF No. 13.) Petitioners initially alleged that A.J.K. suffered a cerebral stroke, hypertension, global developmental delay, and epilepsy caused in fact by A.J.K.'s Measles, Mumps, and Rubella ("MMR"); varicella; and Influenza ("flu") A and B vaccinations administered on September 29, 2014. (ECF No. 1.) On April 1, 2019,

[1] Because this document contains a reasoned explanation for the action taken in this case, it must be made publicly accessible and will be posted on the United States Court of Federal Claims' website, and/or at https://www.govinfo.gov/app/collection/uscourts/national/cofc, in accordance with the E-Government Act of 2002. 44 U.S.C. § 3501 note (2018) (Federal Management and Promotion of Electronic Government Services). **This means the document will be available to anyone with access to the internet.** In accordance with Vaccine Rule 18(b), Petitioner has 14 days to identify and move to redact medical or other information, the disclosure of which would constitute an unwarranted invasion of privacy. If, upon review, I agree that the identified material fits within this definition, I will redact such material from public access.

[2] All references to "§ 300aa" below refer to the relevant section of the Vaccine Act at 42 U.S.C. § 300aa-10-34.

petitioners filed an amended petition, now alleging that A.J.K. suffered "posterior reversible leukoencephalopathy or stroke, seizure disorder and their sequelae," caused-in-fact by her MMR, Hepatitis A ("Hep A"), varicella, and flu vaccines administered on September 29, 2014. (ECF No. 56.) Alternatively, petitioners allege "the significant aggravation of an underlying seizure condition and its sequelae caused by" the alleged vaccinations on September 29, 2014. (*Id.*) For the reasons set forth below, I conclude that petitioners are *not* entitled to an award of compensation.

I. Applicable Statutory Scheme

Under the National Vaccine Injury Compensation Program,[3] compensation awards are made to individuals who have suffered injuries after receiving vaccines. In general, to gain an award, a petitioner must make a number of factual demonstrations, including showing that an individual received a vaccination covered by the statute; received it in the United States; suffered a serious, long-standing injury; and has received no previous award or settlement on account of the injury. Finally – and the key question in most cases under the Program – the petitioner must also establish a causal link between the vaccination and the injury. In some cases, the petitioner may simply demonstrate the occurrence of what has been called a "Table Injury." That is, petitioners may show that they suffered an injury of the type enumerated in the "Vaccine Injury Table," corresponding to the vaccination in question, within an applicable time period following the vaccination also specified in the Table. In such cases, the Table Injury is presumed to have been caused by the vaccine. § 300aa-13(a)(1)(A); § 300 aa-11(c)(1)(C)(i); § 300aa-14(a); § 300aa-13(a)(1)(B).

In many cases, however, the vaccine recipient may have suffered an injury not covered by the Vaccine Injury Table. In these "off-Table" cases, an alternative means exists to demonstrate entitlement to a Program award. The petitioner may demonstrate entitlement by showing that the recipient's injury was "caused-in-fact" by the vaccine they received, a showing often referred to as "actual causation." § 300aa-13(a)(1)(B); § 300aa-11(c)(1)(C)(ii). In off-table cases, the presumptions available under the Vaccine Injury Table are inoperative, and the burden is on the petitioner to introduce evidence demonstrating that the vaccination was responsible for the injury in question. *Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274, 1278 (Fed. Cir. 2005); *Hines v. Sec'y of Health & Human Servs.*, 940 F.2d 1518, 1525 (Fed. Cir. 1991). Because the injuries petitioners alleged are not listed as Table Injuries relative to any of the vaccinations at issue, petitioner must meet the burden of proof for an off-Table, or "cause-in-fact" claim. *See* 42 C.F.R. § 100.3(a).

To show actual causation, petitioner must satisfy the "preponderance of the evidence" standard, the same standard ordinarily used in tort litigation. § 300aa-13(a)(1)(A); *see also Althen*, 418 F.3d at 1279; *Hines*, 940 F.2d at 1525. Under that standard, the petitioner must show that it is "more probable than not" that the vaccination caused the alleged injury. *Althen*, 418 F.3d at 1279. The petitioner need not show that the vaccination was the sole cause of the injury or condition but must

[3] The National Vaccine Injury Compensation Program is hereinafter referred to as the "Program."

demonstrate that the vaccination was a "substantial factor" and a "but for" cause. *Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352 (Fed. Cir. 1999). This standard has been interpreted to require "proof of a logical sequence of cause and effect showing that the vaccination was the reason for the injury;" the logical sequence must be supported by "reputable medical or scientific explanation, *i.e*., evidence in the form of scientific studies or expert medical testimony." *Althen*, 418 F.3d at 1278; *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). A petitioner may not receive a Vaccine Program award based solely on his or her assertions; rather, the petition must be supported by either medical records or by the opinion of a competent physician. § 300aa-13(a)(1).

In what has become the predominant framing of this burden of proof, the *Althen* court described the "causation-in-fact" standard, as follows:

> Concisely stated, Althen's burden is to show by preponderant evidence that the vaccination brought about her injury by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of proximate temporal relationship between vaccination and injury. If Althen satisfies this burden, she is "entitled to recover unless the [government] shows, also by a preponderance of the evidence, that the injury was in fact caused by factors unrelated to the vaccine."

Althen, 418 F.3d at 1278 (citations omitted). The *Althen* court noted that a petitioner need not necessarily supply evidence from medical literature supporting petitioner's causation contention, so long as the petitioner supplies the medical opinion of an expert. *Id*. at 1279-80. That expert's opinion must be "sound and reliable." *Boatmon v. Sec'y of Health & Human Servs*., 941 F.3d 1351, 1359-60 (Fed. Cir. 2019). The *Althen* court also indicated, however, that a Program fact finder may rely upon "circumstantial evidence," which the court found to be consistent with the "system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants." *Althen,* 418 F.3d at 1280.

Where a petitioner in an off-Table case is seeking to prove that a vaccination aggravated a pre-existing injury, petitioners must also establish three *additional* factors. *See Loving v. Sec'y of Health & Human Servs.*, 86 Fed. Cl. 135, 144 (Fed. Cl. 2009) (combining the first three *Whitecotton* factors for claims regarding aggravation of a Table injury with the three *Althen* factors for off table injury claims to create a six-part test for off-Table aggravation claims); *see also W.C. v. Sec'y of Health & Human Servs.*, 704 F.3d 1352, 1357 (Fed. Cir. 2013) (applying the six-part *Loving* test.). The additional *Loving* factors require petitioners to demonstrate aggravation by showing: (1) the vaccinee's condition prior to the administration of the vaccine, (2) the vaccinee's current condition, and (3) whether the vaccinee's current condition constitutes a "significant aggravation" of the condition prior to the vaccination. *Id*.

II. Procedural History

This case was first assigned to another special master. (ECF No. 5.) As noted above, petitioners initially alleged A.J.K. suffered a stroke. (ECF No. 1.) Between January and March of 2018, petitioners filed medical records marked as Exhibits 1-21. (ECF Nos. 15-16, 20-21.) Respondent then filed his Rule 4 Report on May 31, 2018, arguing that the evidence presented did not meet petitioner's burden and recommending against compensation. (ECF No. 27.) Thereafter, petitioners continued to compile evidence, including additional medical records marked as Exhibit 22, as well as videos of A.J.K. filed as Exhibit 23. (ECF Nos. 28, 36.)

On December 10, 2018, petitioners filed an expert report drafted by pediatric neurologist AHM Mahbubul Huq, MBBS, Ph.D. (ECF No. 38; Exs. 24-25; *see also* Exs. 26-41, 43-84, 86-111, 113-24, 126-29 (cited literature).) Dr. Huq opined that A.J.K. suffered either a stroke or a condition known as "posterior reversible leukoencephalopathy syndrome" ("PRES") and couched his causation opinion largely as relating to PRES. (Ex. 24.) On February 27, 2019, the special master held a status conference, suggesting that petitioner file an amended petition, given that Dr. Huq's expert report expanded on A.J.K.'s alleged injuries. (ECF No. 51.) Petitioners filed additional medical records marked as Exhibits 130-131 on March 18, 2019, and an amended petition on April 1, 2019, adding an allegation that A.J.K.'s vaccinations caused PRES. (ECF Nos. 55-56.) Meanwhile, respondent filed an expert report by immunologist Thomas G. Forsthuber, M.D., Ph.D. (ECF No. 52, Ex. A-B; *see also* Ex. A Tabs 1-22 (cited literature)) and, later, an expert report by pediatric neurologist Peter M. Bingham, M.D. (ECF No. 59, Ex. C-D; *see also* Ex. C Tabs 1-5 (cited literature)).

Thereafter, this case was reassigned to my docket on August 27, 2019. (ECF No. 64.) Petitioners then filed a supplemental report by Dr. Huq (ECF No. 65; Ex. 133), updated medical records (ECF No. 67; Ex. 132), an expert report by immunologist M. Eric Gershwin, M.D. (ECF No. 68, Ex. 147), and medical literature marked as Exhibits 134-146 and 148-164 (ECF Nos. 70-76.). Respondent responded with supplemental reports by Dr. Forsthuber (ECF Nos. 77-78; Ex. E; *see also* Ex. E, Tabs 1-17 (cited literature)) and Dr. Bingham (ECF No. 79; Ex. F; *see also* Ex. F, Tab 1 (cited literature)). On March 17, 2020, I held a status conference, during which I urged petitioners' experts to further address the relationship, if any, between vaccination, inflammation, hypertension, and PRES. (ECF No. 80.) Petitioners filed further reports from each of their experts (ECF Nos. 82-83; Exs. 165-66), and then respondent filed a supplemental report by Dr. Forsthuber (ECF No. 84; Ex. G; *see also* Ex. E, Tabs 1-10 (cited literature)). At that point, an entitlement hearing was set. (ECF Nos. 89, 95.)

On February 15, 2021, petitioners filed a supplemental expert report from Dr. Gershwin, medical literature, and medical records from Mount Washington Pediatric Hospital. (ECF Nos. 90-94; Exs. 165-94.) The parties then filed another round of supplemental immunology expert reports. (ECF No. 97; Ex. H (Dr. Forsthuber), ECF No. 99; Ex. 195 (Dr. Gershwin).) I then issued a Non-PDF order indicating that the "record of this case is now presumptively complete for purposes of proceeding to the

entitlement hearing…[and] if either party wishes to raise any issue in the interim, they should file a status report or otherwise contact chambers." (Non-PDF Scheduling Order, filed July 9, 2021.)

Subsequently, petitioners refiled literature, highlighted for hearing, as Exhibits 196-224. (ECF No. 102-04.) Petitioners also filed additional medical records (ECF Nos. 104, 113; Exs. 225-26) and several additional pieces of medical literature (ECF Nos. 108, 111; Exs. 227-31). On July 11, 2022, respondent and petitioners filed their prehearing briefs. (ECF Nos. 124, 126.) Mrs. Kaltenmark's declaration was filed on July 18, 2022. (ECF No. 134, Ex. 234.)

A two-day entitlement hearing was held remotely on July 20 and 21, 2022, via Webex. (*See* ECF Nos. 139-40 (Transcript of Proceedings ("Tr"), filed August 4, 2022).) Danielle Kaltenmark and all four of the parties' experts testified. The parties agreed to waive post-hearing briefs. (Tr. 408.) On August 22 and November 22, 2022, petitioner filed updated medical records from A.J.K.'s pediatrician and current neurologist. (ECF Nos. 142, 146.)

This case is now ripe for a decision on entitlement.

III. Issues to be Decided

As the factual history below demonstrates, A.J.K. has an extensive medical history. However, much of that medical history is effectively undisputed. Respondent's neurology expert, Dr. Bingham, agrees that A.J.K. suffered an acute neurologic event of some kind in early October of 2014, at just over one year of age and about two days after administration of the vaccinations at issue. He further agrees that this acute neurologic event explains A.J.K.'s current condition, including her epilepsy and developmental delay. (Tr. 308-09.) Instead, it is the nature of the acute event—and whether it was vaccine-caused—that must be addressed.

Petitioners contend that the acute neurologic event was PRES, which resulted from a cytokine response to vaccination that acted synergistically with a preexisting infection of hand foot and mouth disease ("HFMD" or "HFM infection"). PRES is a clinical and radiological syndrome in which vasogenic edema is found predominantly in the bilateral parieto-occipital regions of the brain resulting in acute neurologic deficits. (Ex. 68, p. 1; Ex. C, Tab 4, p. 1.) Petitioners assert that, to the extent A.J.K. likely suffered a stroke, the stroke occurred in the context of, and as a result of, the PRES. (ECF No. 126, pp. 14-15.) Petitioners contend they have preponderantly demonstrated each of the three *Althen* prongs. (*Id*. at 13-28.)

Respondent contends that A.J.K.'s acute neurologic event was a stroke that resulted from documented hypertension and was unrelated to her vaccinations. Respondent's experts further contend that A.J.K.'s HFM infection would be a more likely contributor to her stroke than her vaccinations (Tr. 288 (Dr. Bingham); Tr. 324 (Dr. Forsthuber)); however, respondent does not argue that he could meet his own burden

of proof of demonstrating that the HFMD is a more likely cause of A.J.K.'s injury as a factor unrelated to vaccination. (ECF No. 124, pp. 20-27.) Respondent disputes that petitioners have preponderantly demonstrated any of the three *Althen* prongs. (*Id*.)

IV. Factual History

a. As reflected in the medical records

i. Pre-vaccination records

A.J.K. was delivered at full-term by vaginal delivery on September 26, 2013. (Ex. 3, p. 243.) She weighed nine pounds, four ounces, at birth. (*Id*.) A.J.K.'s Apgar scores were nine and nine, respectively. (*Id*.) A.J.K. failed her initial hearing screen. (*Id.* at 483.) However, she passed an Auditory Brainstem Response test at the time of her first newborn checkup. (Ex. 3, pp. 381-85, 483-84.) In December of 2013, she was hospitalized for an RSV infection and bronchiolitis. (Ex. 3, pp. 45, 361, 365, 367-70.) Throughout early 2014, A.J.K. sought treatment with her pediatrician for mild asthma, wheezing exacerbations, bronchiolitis, viral rashes, and mild reflux. (Ex. 3, pp. 337, 347, 355-58; Ex. 16, p. 1.) On May 13, 2014, A.J.K. was assessed with reactive airway disease. (Ex. 3, p. 335.) During A.J.K.'s nine-month well visit, on July 3, 2014, she was noted to have "borderline gross motor skills" on evaluation. (*Id.* at 323-28.)

About two weeks prior to the vaccinations at issue, A.J.K. presented for care for what was diagnosed as HFMD. Specifically, on September 17, 2014, A.J.K.'s mother contacted the pediatrician's office and reported that A.J.K. developed a rash "from head to toe" and had been "super cranky" for approximately one day. (Ex. 3, p. 322.) A.J.K. had "red dots" and a larger rash on her hands and face with an elevated temperature of 102.7° F. (*Id*.) On September 21, 2014, A.J.K. sought evaluation for her fever of 101.7° F for two days, and a red rash that was becoming worse on the trunk and all her extremities. (Ex. 3, pp. 318-20.) A.J.K. also had a runny nose. (*Id*.) A.J.K. was diagnosed with HFMD and treated symptomatically. (*Id*.)

On September 29, 2014, A.J.K. presented to Katharyn Turner, M.D., for her 12-month well-check visit. (Ex. 3, pp. 310-17.) A.J.K. was growing and developing appropriately for her age, and although A.J.K.'s "ages and stages questionnaire" reflected "borderline" gross and personal-social skills, there were "no concerns during the exam." (*Id*. at 315-16.) A.J.K.'s mother raised a concern regarding "twitching," which was assessed to be benign myoclonus of infancy or sleep myoclonus.[4] (*Id.* at

[4] Specifically, A.J.K.'s mother reported that "during sleep or just as [A.J.K.] is falling asleep she will at times have twitching or movement of her arms, flexion at the elbow or wrist." (*Id*. at 312.) Dr. Turner further recorded that "[t]his does not persist and parents call these movement[s] intermittent." (*Id*.) Dr. Turner indicated that "the description sounds more like benign myoclonus of infancy or sleep myoclonus," though she discussed seizure precautions and red flags. (*Id.* at 316.) Although some subsequent histories appear to accept the reports of these earlier episodes of twitching as the onset of seizures (*e.g*. Ex. 7, p. 1), both parties' neurology experts ultimately testified that they agree with Dr. Turner's diagnosis and indicate that myoclonus would be distinct from A.J.K.'s later seizure disorder attributable to her acute

312, 316.) A.J.K. was doing well following her prior HFM infection, with only "faint remnants of the rash." (*Id*. at 315.) In connection with this visit, A.J.K. received the MMR, varicella, flu, and Hep A vaccinations at issue in this case. (Ex. 1, p. 1.)

ii. Acute event and hospitalization

Two days after the subject vaccinations, at around noon on October 1, 2014, A.J.K.'s mother contacted the pediatrician and reported that A.J.K. had been "twitching and lethargic" since the night before and vomited that day. (Ex. 3, p. 309.) A.J.K. was reportedly "just laying around like she is sleeping and has not made a sound." (*Id*. (cleaned up).) The pediatrician's office documented that A.J.K.'s twitching was the same as had been previously reported. (*Id.*) A.J.K.'s mother planned to take her to the emergency room.[5] (*Id.*)

A.J.K. presented to South Georgia Medical Center emergency department at around 1:00PM the same day. (Ex. 9, p. 17.) Her temperature was normal. (*Id*. at 56.) While in the emergency department, A.J.K. was nonresponsive to verbal stimuli and the parents reported she was "not acting appropriate." She was observed to have an episode of lip and right arm twitching and was administered Ativan[6] and was also oxygenated. (*Id*. at 57.) On physical exam she was noted to be unresponsive and in severe distress. She was tachycardic, experiencing respiratory distress, and was disoriented. (*Id*. at 58.) EKG, chest x-ray, head CT, toxicology screen, and lumbar puncture were all unremarkable, except that the CT scan showed moderately severe pansinusitis. (Ex. 9, pp. 48, 62, 67-68, 74-75.) The chest x-ray showed haziness in the perihilar regions, interpreted as likely bronchiolitis. (*Id*. at 7.) She was negative for influenza A and B and respiratory syncytial virus ("RSV"). (*Id*. at 26-27.) Dr. Joseph Tresmonte (pediatric neurology) was consulted by telephone and A.J.K. was placed on Keppra[7] and Fosphenytoin[8] at his request. (*Id*. at 57, 59.) A.J.K. was subsequently

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neurologic event. (Tr. 75-76 (Dr. Huq); Tr. 278-80, 298-99 (Dr. Bingham).) Accordingly, the conflicting histories will not be discussed in detail, though they have been reviewed.

[5] Dr. Turner wrote a follow-up note at 2:54PM likewise recommending that petitioner take A.J.K. to the emergency department; however, A.J.K. had already been admitted by the time this note was recorded. (*Compare* Ex. 3, p. 309, *with* Ex. 9, p. 17).

[6] Ativan is the brand name for lorazepam, which is a benzodiazepine that is administered intravenously to control status epilepticus. *Lorazepam*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=28747 (last visited Nov. 7, 2023). Benzodiazepines act as depressants of the central nervous system; they have antianxiety, sedative, anticonvulsant, and muscle relaxing effects. *Benzodiazepine*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=5838 (last visited Nov. 7, 2023).

[7] Keppra is the brand name for levetiracetam, which is an orally administered anticonvulsant treatment of any seizure due to a lesion in a specific, known area of the cerebral cortex, as well as idiopathic generalized epilepsy. *Levetiracetam*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=28136 (last visited Nov. 7, 2023).

[8] Fosphenytoin is the prodrug of phenytoin. *Fosphenytoin sodium*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=19138 (last visited Nov. 7, 2023); *see also*

observed to have stable vitals and no specific complaints. She was discharged around 8:00PM. (*Id*. at 57.) Her diagnoses were sinus tachycardia, respiratory distress, rhonchi, and generalized seizures. Petitioners were directed to follow up with A.J.K.'s primary care provider for a specialist referral. (*Id*. at 59.)

However, shortly after discharge, A.J.K. was transported by ambulance back to the emergency room when she began "gazing up and to the right," developed lip smacking, and mild twitching. (Ex. 10, pp. 2-3; Ex. 7, p. 10.) The paramedic observed that A.J.K. had a fever. (Ex. 9, p. 34.) At the emergency department, A.J.K. had a temperature of 100.8° F, and she was administered Rocephin[9] and fluids at the hospital. (Ex. 10, pp. 2-3.) As of 10:13PM, A.J.K.'s blood pressure was recorded at 123/63, which is high for a 12-month-old. (Ex. 9, pp. 32-33; Tr. 285.) At about 11:30PM, she was transferred by ambulance to the Medical Center of Central Georgia and into the care of Dr. Trasmonte. (Ex. 9, p. 38; Ex. 7, p. 1.) Dr. Trasmonte instructed that A.J.K. should be administered 20mg/kg of phenobarbital prior to transfer. (Ex. 10, p. 2.) During the transfer, A.J.K.'s blood pressure was measured eight times over the course of about two hours.[10] (*Id.* at 38-39.) After transfer, she remained hospitalized from October 2 to October 7, 2014. (Ex. 7, p. 1.)

Upon admission to the Medical Center of Central Georgia, aspirin was started as a stroke prophylaxis. (*Id.*) An MRI of the brain showed abnormal bioccipital cortical hyperintensity with restricted water diffusion on diffusion weighted imaging. The radiologist's impression included a differential diagnosis of post ictal state, PRES, ischemia, or encephalitis. (*Id*. at 51.) Additionally, an EEG showed diffuse background slowing consistent with an underlying non-specific disturbance of neuronal function. (*Id*. at 48.) It was also noted the EEG result may be explained as a drug effect. (*Id*. at 54.)

A.J.K. had a neurology consultation with Dr. Trasmonte on the morning of October 3, 2014.[11] (*Id.* at 1-2.) Dr. Trasmonte concluded the MRI findings were consistent with bilateral occipital acute ischemic stroke. (*Id.*) He explained:

Prodrug, STEDMAN'S MEDICAL DICTIONARY (28th ed. 2006) (defining a prodrug as a class of drugs requiring conversion by metabolic processes within the body to produce pharmacologic action). Phenytoin is an orally administered anticonvulsant that is used to treat status epilepticus. *Phenytoin*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=38541 (last visited Nov. 7, 2023).

[9] Rocephin is the brand name of ceftriaxone sodium, which is an intravenously or intramuscularly administered antibiotic, specifically a "semisynthetic, β-lactamase-resistant, broad-spectrum, third-generation cephalosporin," that is effective against a wide range of bacteria. *Ceftriaxone sodium*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=8471 (last visited Nov. 7, 2023).

[10] Specifically: 100/52 at 1:06AM, 102/45 at 1:18AM, 97/51 at 1:31AM, 95/43 at 1:47AM, 97/45 at 2:06AM, 101/45 at 2:28AM, 99/47 at 2:47AM, and 96/42 at 3:10AM. (Ex. 9, pp. 38-39.)

[11] Among his notes, Dr. Trasmonte documented a "strong family history of stroke in the young." (Ex. 7, p.1.) However, Mrs. Kaltenmark testified that the entry is not correct. (Tr. 61.) There are also inconsistent notations in the medical records regarding whether there is a family history of seizures. (*Compare* Ex. 7, p. 1, *with* Ex. 3, p. 303.)

> We [will] look for an underlying etiology by performing a comprehensive workup. However we do note that a vast majority of patients do not have a clear underlying cause (idiopathic). I am very concerned about the possibility of a vessel abnormality such as dissection because of the posterior distribution of the ischemia. We [will also] begin stroke prophylaxis using ASA. The other part of the differential of bioccipital hyperintensity on T2/FLAIR is PRES (posterior reversible encephalopathy syndrome). Typically however in PRES the diffusion weighted images would show either equivocal findings or if it is bright usually the ADC mapping images would not be dark as seen in this patient.

(*Id*. at 2.) Dr. Trasmonte noted that he had an extended discussion with A.J.K.'s mother during which he characterized the diagnosis of stroke as a "working impression" based on the preponderance of the clinical and radiologic evidence. (*Id*.) A follow-up MRA of the head and neck was normal. (*Id*. at 49.) Ultimately, her discharge diagnosis was "bilateral posterior ischemic stroke" without indication of an underlying cause. (*Id*. at 14.)

A summary from A.J.K.'s sixth day of hospitalization indicated that "BPs continue to have some elevations into range of 99th percentile. (91/46 . . . 117/63 . . . 103/63 . . . 100/54 today)." After noting that workup has been within normal limits ("nl"), it further explains that "[s]everal of the higher BPs were taken when child is fussing. Plan was to monitor closely overnight with BPs every 4 hrs and document if child agitated or not." (*Id*. at 18.) Dr. Blackwood of pediatric cardiology was to review the results and provide further consultation. (*Id*.) Around that same time, A.J.K.'s father reported to Dr. Turner, the primary care provider, that A.J.K. would remain hospitalized until October 9 and that hypertension was suspected as the cause of A.J.K.'s stroke. (Ex. 3, p. 307.) Subsequently, however, A.J.K. was discharged on October 7. On the day of discharge, Dr. Trasmonte conducted a follow-up consultation during which he noted that "[t]here was concern over the weekend that her blood pressures are high . . . . Cardiology was consulted and they agreed that she is not hypertensive." (Ex. 7, p. 6.) Although she was later placed on lisinopril[12] for hypertension, she was not treated for hypertension prior to discharge. (*See, e.g.*, Ex. 12, p. 5.)

iii. Follow-up care

After discharge, A.J.K. returned for several visits with her primary care provider, beginning on October 8, 2014. (Ex. 3, pp. 302-06.) Dr. Turner noted that since discharge, A.J.K. was "almost to baseline," though she had been more agitated lately, which her parents attributed to the Keppra. (*Id.* at 303.) The next day, on October 9, 2014, A.J.K. again presented to Dr. Turner with a one-day history of rash covering her entire body, except the lower legs, with no fever or scratching. (*Id.* at 296.) It was

[12] Lisinopril is an orally administered "angiotensin-converting enzyme inhibitor" that is used to treat hypertension, as well as congestive heart failure and acute myocardial infarction. *Lisinopril*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=28515 (last visited Nov. 7, 2023).

noted that she had rhinorrhea and the rash was attributed to viral exanthem. No further action was needed apart from monitoring. (*Id*.at 298.) On October 15, 2014, A.J.K. presented for another post-hospitalization evaluation with Dr. Turner. (*Id.* at 304-306.) At that time, A.J.K.'s family reported that she was "back to her normal self," with the exception of continued right-sided weakness and diminished physical activity but was improving. (*Id*. at 306.)

On October 20, 2014, A.J.K. presented for an initial physical therapy evaluation. (Ex. 13, pp. 7-9.) She exhibited developmental delays in locomotion skills, and one year of twice weekly physical therapy was recommended. (*Id.* at 8-9.) The physical therapist noted that A.J.K.'s older brother was a late walker and her older sister received speech therapy. (*Id.* at 7.) On October 27, 2014, A.J.K. presented for an initial evaluation for occupational therapy. (*Id.* at 1-2.) A.J.K.'s assessment noted no significant motor or adaptive delays, and skilled services were not needed at that time. (*Id.*) That same day, A.J.K. also began speech therapy. (*Id.* at 4-5.) A.J.K. responded to her name but did not use any words. (*Id.* at 5.) Based on formal test scores and clinical opinion, she exhibited a moderate language impairment. (*Id.*) Speech therapy was recommended. (*Id.*)

On November 4, 2014, A.J.K. presented for evaluation at Sibley Heart Center Cardiology. At her initial encounter, she saw Wesley Blackwood, M.D. (Ex. 12, p. 5-7.) The chief complaint was "elevated blood pressure." (*Id*. at 5.) The history indicated A.J.K. suffered multiple seizures and embolic strokes. She was noted to have had "borderline elevated blood pressure in the hospital but blood work, UA, echocardiogram and renal ultrasound were all normal. She was not started on anti-hypertensive therapy prior to discharge." Dr. Blackwood noted there is no family history of hypertension. (*Id*.) At this encounter, A.J.K.'s systolic blood pressure was 140 mmHg when measured at the right upper extremity and 110 mmHg when measured at the left lower extremity. In both instances, however, it was noted that there was "lots of moving." (*Id*.) An ECG was performed due to concern for hypertensive changes. (*Id.* at 7.) The ECG showed sinus rhythm; normal axes, intervals and voltages for her age; and no evidence of left ventricular hypertrophy. (*Id.*) Dr. Blackwood concluded that A.J.K.'s blood pressure was significantly elevated and diagnosed Stage II systolic hypertension. (*Id*.) However, he indicated that there does not appear to be any organic cause for her hypertension. He further indicated that the blood pressure elevation "could certainly be a result of her recent neurologic issues and cardiovascular dysregulation." (*Id*.) A.J.K. was started on lisinopril, and she was to return in 3 weeks. (*Id*.)

On December 1, 2014, A.J.K. returned to the Sibley Heart Center and saw Dr. Benjamin Toole. (*Id.* at 1.) Systolic blood pressure was 132 mmHg, but she was noted to be "crying and kicking." (*Id*.) Dr. Toole noted that "it is difficult to tell if [A.J.K.'s] BP remains elevated at baseline (she was agitated today)." (*Id.* at 2.) However, he advised that, given her history, it would be "reasonable" to increase her dose of lisinopril. (*Id*.) Dr. Toole reiterated that no organic cause for A.J.K.'s hypertension had been identified and that it "could certainly be" a result of her neurologic issues and cardiovascular dysregulation. (*Id.*)

On December 21, 2014, A.J.K returned to Dr. Turner for a refill of Keppra and repeat MRI (brain) and MRA (head and neck imaging). (Ex. 3, pp. 283-87.) A.J.K. was also taking vitamin B6 because she was exhibiting aggression while on Keppra. (*Id.* at 283.) She was now walking, with nearly full use of her right leg, slight high stepping with no foot drop. (*Id.*) A.J.K was starting to babble more, she was continuing physical therapy, and "[s]he has had no seizures." (*Id.*)

On January 27, 2015, A.J.K. underwent an MRA of the head and neck without contrast and MRI of the brain without contrast. (Ex. 15, pp. 3-6.) Her brain MRI showed (1) resolved bilateral occipital diffusion restriction, with sequelae on T2 and FLAIR throughout the same distribution, in keeping with developing gliotic changes and encephalomalacia in the region of previous ischemia and cortical infarction; (2) no acute process; and (3) inflammatory signal changes in the sinuses. (*Id.* at 4.) A.J.K's head and neck MRA were normal. (*Id.* at 3, 6.)

The next day, January 28, 2015, A.J.K. presented to Dr. Turner for her 15-month well-check. (Ex. 3, pp. 271-77.) It was noted that A.J.K. was discharged from physical therapy after having met her goals. (*Id.* at 273.) Her mother declined A.J.K.'s 15-month vaccinations because "they still don't have a reason for the stroke and [she] is waiting for more information before going ahead with vaccines." (*Id.*) A.J.K.'s ages and stages scores were as follows: communication 20/60, gross motor 40/60, fine motor 20/60, problem solving 40/60, and personal/social skills 25/60. (*Id.* at 276.) Dr. Turner felt that A.J.K. was improving with regard to development but was still behind. (*Id.* at 277.)

iv. Medical care after relocation to Texas

On February 13, 2015, A.J.K. presented for treatment with a new pediatrician following her family's move from Georgia to Texas. (*Id.* at 262-64.) John Poulin, M.D., noted that A.J.K. had not been seen by genetics, and he documented that A.J.K. still had tonic clonic seizures approximately once a month, which were "usually associated with [upper respiratory infection] or illness." (*Id.* at 262.) Regarding the seizure and stroke, Dr. Poulin remarked, "Association vs causation unknown but potential post imm encephalopathy in [differential diagnosis]." (*Id.* at 264.) He recorded no family history of epilepsy or early stroke. (*Id.* at 262.)

On March 4, 2015, A.J.K. presented for an evaluation with the developmental pediatrics service. (*Id.* at 257-60.) In the Reason for Visit section, nurse practitioner Lorraine Howard, APRN, MSN, indicated that A.J.K was referred by Dr. Poulin to assess developmental status for A.J.K. "who experienced seizure, stroke, [hypertension] and developmental delay 2 days after 12-month immunizations." (*Id.* at 258.) A.J.K. was assessed with delayed milestones and instructions to return within two weeks. (*Id.* at 259.) NP Howard provided information about the National Vaccine Injury Compensation Program. (*Id.*)

On March 24, 2015, A.J.K. presented for an evaluation with a new cardiologist, Scott Bentley, M.D. (*Id.* at 251-53.) Dr. Bentley noted that A.J.K. presented with a past medical history notable for a cerebrovascular accident ("CVA") and subsequent seizures "which occurred 2 days after receiving her 1[2] month immunizations." (*Id.* at 251.) On examination, all other systems were negative. (*Id.*) Dr. Bentley observed that A.J.K was normotensive. (*Id.* at 252-53.) Reviewing A.J.K.'s notes from her previous cardiologists, Dr. Bentley observed that her highest pressures were in the earliest time after her CVA. (*Id.* at 253.) Dr. Bentley "wonder[ed] if this was precipitated by her event and now that we are further away from that event, she might not need to continue medication indefinitely." (*Id.*) Dr. Bentley planned to continue A.J.K. on lisinopril at her current dose, but instructed her to return in October, a year after her last echocardiogram. (*Id.*)

That same day, A.J.K. presented for a neurology evaluation with David Hsieh, M.D. (*Id.* at 254-56.) On examination, Dr. Hsieh noted that A.J.K.'s movements were symmetric, and that "watching her spontaneously play, she seems to be moving both sides well now." (*Id.* at 255.) A.J.K. had had no seizures in over a month since increasing her Keppra dosage. (*Id.*) Dr. Hsieh remarked that A.J.K. had been having seizures monthly—three in October, two in November, and one in December. (*Id.*) He requested all of A.J.K.'s records and noted that A.J.K. needed to be evaluated for continued use of lisinopril. (*Id.* at 256.) Dr. Hsieh instructed A.J.K.'s mother to continue her current dose of Keppra. (*Id.*)

On March 25, 2015, A.J.K.'s mother called for an evaluation with the Vaccine Health Center at Fort Belvoir Community Hospital for a possible vaccine adverse event. (*Id.* at 250.) A.J.K.'s mother reported that A.J.K regained all her manual skills but could not speak and "cries a lot because she cannot speak to voice needs." (*Id.*) A.J.K.'s mother suggested the possibility that A.J.K.'s vision "may be somewhat impaired." (*Id.*) Before her 12-month vaccines, A.J.K.'s mother reported that she "twitched" sometimes just before falling asleep, although her "[p]ediatrician said this was normal" and noted that A.J.K.'s "only other illness had been RSV." (*Id.*) Her mother was given information about the Vaccine Injury Compensation Program. (*Id.*)

On April 13, 2015, A.J.K. was evaluated by Stephen Greefkens, M.D., a developmental pediatrician. (*Id.* at 242-45.) Dr. Greefkens observed that A.J.K.'s seizures and hypertension appeared to be well controlled. (*Id.* at 242.) At that time, A.J.K.'s mother's main concern was speech delay. (*Id.* at 243.) Petitioners reported no seizures since January 2015. (*Id.*) Dr. Greefkens noted no family history of neurologic disorders, seizures, or birth defects, but noted A.J.K.'s maternal grandmother was diagnosed with Asperger's syndrome. (*Id.*) Dr. Greefkens recommended that A.J.K. continue her early childhood intervention services. (*Id.* at 245.)

On April 15, 2015, Dr. Hsieh conducted a telephone consultation with petitioners after reviewing A.J.K.'s brain MRI and MRAs. (*Id.* at 241.) In the brain MRI from October 2014, Dr. Hsieh noted restricted diffusion cortically bilateral occipital lobes, left more than right, "but seems mostly restricted to the cortex, and not in the distribution of

the PCA territory and no lesion in the brainstem." (*Id.*) He noted, "[t]o me this appears more consistent with metabolic etiology such as mitochondrial disease or PRES." (*Id.*) He agreed that A.J.K.'s MRA looked normal. (*Id.*) Dr. Hsieh indicated that A.J.K.'s blood pressure on presentation was unclear, though there were some documented blood pressure readings between 109-141/60-79. (*Id.*) A.J.K.'s MRI from January 27, 2015, showed some residual scarring in the occipital lobes, but without new lesions. (*Id.*) Dr. Hsieh recommended weaning the aspirin dosage, as he did not think there was evidence of a PCA distribution ischemic stroke on A.J.K.'s prior imaging. (Ex. 5, p. 229.) He ordered repeat images, including MR spectroscopy, "mainly looking for lactate peak to support mitochondrial disease." (*Id.*)

On April 27, 2015, A.J.K. presented to Luis Rohena, a genetics specialist. (Ex. 3, pp. 236-39.) In the discussion portion, Dr. Rohena noted "[A.J.K.] is a 19-month-old with prior history of seizure activity/stroke 2 days post administration of the MMR vaccine. Encephalopathy post MMR has been described and this may be related to a side effect of the vaccination." (*Id.* at 239.) A.J.K.'s physical exam was concerning for epicanthal folds bilaterally, which Dr. Rohena did not observe in either parent. (*Id.*) Dr. Rohena ordered an SNP DNA microarray to rule out segmental aneuploidy, "especially in the setting of 4 maternal miscarriages." (*Id.*) Results from the chromosomal microarray analysis were normal. (Ex. 5, p. 258.)

On April 30, 2015, A.J.K. underwent a repeat hearing evaluation and the test results were suggestive of normal or near normal hearing. (Ex. 3, pp. 230-31.) A sedated auditory brainstem response ("ABR") was recommended for further evaluation. (*Id*.) On May 4, 2015, A.J.K. underwent a repeat brain MRI, which displayed no significant new findings. (*Id.* at 57-58.) On May 12, 2015, A.J.K. presented for another speech therapy evaluation. (*Id.* at 223-26.) On evaluation, her receptive language was rated at age 12 months and her expressive language was rated at 10 months (at 19 months old). (*Id.* at 224.) A.J.K.'s overall rating was poor. (*Id.*) She was instructed to continue speech therapy and return to the clinic in six months. (*Id.*)

On May 21, 2015, A.J.K.'s mother contacted Dr. Hsieh's office reporting concerns that A.J.K. was spacing out, smacking her lips, and having possible seizures. (*Id.* at 222.) A.J.K.'s speech therapist observed this behavior and was concerned that "they may be absence sz." (*Id.*) Mother reported that A.J.K. does this daily, and more than once a day, but was not keeping count and did not know how long this activity had been going on. (*Id.*) An EEG was ordered, which showed normal results. (*Id.* at 220-21.)

On June 10, 2015, A.J.K. presented for ABR testing, which reflected that her hearing was within normal limits. (*Id.* at 214-19.) There was no evidence of neuropathy or dyssynchrony. (*Id.* at 219.)

On August 13, 2015, A.J.K. returned to genetic specialist Dr. Rohena. (*Id.* at 205-08.) A.J.K.'s mother reported that A.J.K. had had a seizure "2 days after receiving the MMR vaccine at 12 months" and has had 3 total seizures since then. (*Id.* at 206.)

Dr. Rohena observed that A.J.K. "seems to stare off often, raising concerns for Absence Seizures." (*Id.* at 207-08.) He noted that A.J.K.'s recent EEG was normal, though she was not experiencing these staring spells at the time. (*Id.* at 208.) Given these concerns, Dr. Rohena ordered a 70 gene seizure panel. (*Id.*)

On August 19, 2015, A.J.K. presented for a well visit (noted to be an 18-month assessment) with Dr. Hsieh. (*Id.* at 199-203.) A.J.K.'s family declined vaccinations. (*Id.*) The next day, A.J.K.'s father called her pediatrician to report that A.J.K. was jerking her arms and legs when falling asleep. (*Id.* at 198.) He described "1 second jerks, a few random. No further jerking while asleep. Last 3 days. No symptoms during the daytime." (*Id.*) Her father agreed to wait and see if A.J.K.'s condition improved, and if not, then a repeat EEG could be ordered. (*Id.*) The parents were also directed to capture a video of the activity. (*Id.*)

On August 30, 2015, A.J.K. presented to the emergency room for one episode of a witnessed generalized seizure that lasted about four to five minutes in the car. (Ex. 5, pp. 175-76.) A.J.K.'s post ictal state lasted another ten to fifteen minutes. (*Id.* at 175.) A.J.K.'s mother reported drooling and bilateral upper extremity myoclonus. (*Id.*) The record indicates "[d]o not believe meningitis, infectious or traumatic causes." (*Id.*) The hospital physician increased A.J.K.'s Keppra dosage and discharged her home. (*Id.* at 176.)

On October 27, 2015, A.J.K. received an influenza vaccination. (Ex. 1, p. 1.) On November 2, 2015, she presented for a two-year well child visit with Dr. Poulin. (Ex. 3, p. 187-90.) Dr. Poulin noted that A.J.K. had improved in speech and occupational therapies, and was otherwise in good health. (*Id.* at 187-88.) Per A.J.K.'s mother, her speech was improving but not yet up to an age appropriate level. (*Id.* at 188.) Her mother elected to complete one vaccination at a time.[13] (*Id.*)

On November 16, 2015, A.J.K. was admitted to the hospital for possible seizure-like activity, left-sided weakness, and concern for stroke. (Ex. 5, p. 316-22.) A.J.K.'s differential diagnoses included transient ischemic attack, small stroke, viral meningitis and Todd's paralysis post seizure.[14] (*Id.* at 319.) Todd's paralysis post-seizure was considered most likely. (*Id.*) MRI with spectroscopy, MRA and MRV were ordered to rule out a thrombotic event. (*Id.*) Imaging revealed no evidence of acute ischemia or infarction, unchanged bilateral occipital encephalomalacia from prior infarctions, no

[13] A.J.K.'s vaccination record reflects that the flu vaccine was administered on October 27, 2015. (Ex. 1, p. 1; Ex. 5, p. 316.) However, A.J.K.'s encounter record states that the flu vaccine was administered in connection with the visit of November 2, 2015. (Ex. 3, p. 189.)

[14] Todd's paralysis manifests as a temporary paralysis, lasting no longer than a few days, in the limb or limbs that were involved in "jacksonian epilepsy" after a seizure. *Todd paralysis*, STEDMAN'S MEDICAL DICTIONARY (28th ed. 2006). Jacksonian epilepsy is characterized by focal motor seizures, which are due to a discharging focus in the contralateral motor cortex, with unilateral clonic movements that start in one muscle group before systematically spreading to adjacent muscle groups, "reflecting the march of the epileptic activity through the motor cortex." *Jacksonian epilepsy*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=73459 (last visited Nov. 7, 2023).

evidence for dural venous sinus thrombosis, hypoplastic or stenotic left transverse sinus appeared unchanged, and no evidence of significant vascular narrowing or occlusion on the MRA head and neck. (Ex. 3, p. 176.)

On November 18, 2015, A.J.K. presented for another follow-up genetic evaluation with Dr. Rohena. (*Id.* at 178-80.) Given the prior negative studies, Dr. Rohena recommended whole exome sequencing with mitochondrial genome analysis of the family. (*Id.* at 180.)

On December 7, 2015, A.J.K. presented for a follow-up with Dr. Hsieh. (*Id.* at 174-77.) Dr. Hsieh indicated that A.J.K. seemed to come out of her "staring episodes" easily with stimulation, suggesting the episodes are probably non-epileptic. (*Id.* at 177.) He recommended continued observation and physical, speech, and occupational therapy. (*Id.*) On December 14, 2015, A.J.K. returned to her cardiologist Dr. Bentley. (Ex. 5, p. 93.) A.J.K. had been off blood pressure medication for about a month and her blood pressure was normal. At this encounter, Dr. Bentley formally discontinued treatment for elevated blood pressure. (*Id.* at 95.) A.J.K. was discharged from routine cardiology care and instructed to follow-up only as needed. (*Id.*)

v. Medical care in 2016 and later

On January 13, 2016, A.J.K. presented for a follow-up evaluation with Dr. Greefkens at the developmental clinic. (Ex. 3, pp. 166-69.) A.J.K.'s mother reported no specific concerns. (*Id.* at 167) A.J.K. exhibited delayed play skills and articulation problems. (*Id.* at 168.) Dr. Greefkens recommended a sleep study and continued speech therapy. (*Id.* at 169.) A.J.K.'s subsequent sleep study on January 31, 2016, was normal for sleep abnormalities. (*Id.* at 160.)

On April 5, 2016, A.J.K. returned to Dr. Rohena. (*Id.* at 146-51.) Dr. Rohena noted that the full exome sequencing, bioinformatics, variant filtering, and gene and variant medical review did not reveal any alterations with likely clinical relevance. (*Id.* at 146.) Specifically, no large deletions or known pathogenic mutations were detected in the mitochondrial genome. (*Id.*) Dr. Rohena indicated that "novel gene alterations" could not be ruled out. (*Id.*) No further genetic testing was recommended. (*Id.*)

On April 11, 2016, A.J.K. returned for her neurology follow-up evaluation. (*Id.* at 143-45.) A.J.K.'s right-sided paresis was improved, and her language delays were improving. (*Id.* at 144-45.) Mother indicated that A.J.K. was now using 2 to 3-word phrases and knew approximately 50 words. (*Id.* at 144.) On physical examination, A.J.K. appeared symmetrical and was moving both sides well. (*Id.*)

On June 8, 2016, A.J.K. had an allergy evaluation with Daniel Steigelman, M.D. (*Id.* at 135-37.) A.J.K.'s mother indicated that a VAERS report was completed five months after her CVA. (*Id.*) Dr. Steigelman's assessment included local reactions to insect stings without evidence of anaphylaxis and noted that her CVA two days after vaccines is "rightly concerning for an adverse vaccine reaction but there is no course to

prove or disprove immunizations were causative." (*Id.*) Later that day, A.J.K. presented to the emergency room with an inability to walk and change in speech. (Ex. 5, pp. 60-63.) On physical examination, A.J.K. showed no acute distress and good eye contact. (*Id.* at 61.) A.J.K. was admitted for concern of subacute seizures. (*Id.* at 63.)

On October 5, 2016, A.J.K. presented for her three-year-old well visit. (Ex. 3, pp. 114-17.) A.J.K.'s pediatrician noted that she walks and runs well, but still receives speech therapy and demonstrates delayed fine motor skills. (*Id.* at 115.) A.J.K.'s family indicated that they would resume A.J.K.'s vaccines at age four. (*Id.* at 117.)

On February 27, 2017, A.J.K. returned for a follow-up neurology evaluation with Richard Hussey, M.D. (Ex. 3, pp. 98-100.) At this time, A.J.K.'s staring spells were rare, and she had "no further suspicious overt or subtle seizures." (*Id.* at 99.) A.J.K.'s speech was coming along, though petitioners indicated that she was very shy. (*Id.*) In the prenatal history, Dr. Hussey indicated that A.J.K. was "noted to have twitching prior to her stroke at her 12-month visit, when she received her vaccinations (which have been implicated in her stroke)." (*Id.*) In his assessment, Dr. Hussey indicated that A.J.K. was currently stable, though her history included:

> [R]eported seizure in the setting of stroke with left sided paresis at 12 months old, 2 days after immunizations. [U]nknown etiology, course suspicious for other etiology than vaccination related due to preceding symptoms suggestive of seizures, and lesions may have been outcome of status epilepticus due to the prolonged nature of her symptoms.

(*Id.* at 100.) A.J.K.'s examination was symmetric that day, and Dr. Hussey instructed her to continue Keppra for seizures, Vitamin B6 for behavior, and to continue her therapies. (*Id*.)

Further medical records have been filed documenting A.J.K.'s clinical course through 2022. However, the details of that remaining clinical course are not informative of the issues discussed in this decision. None of the remaining records revisit the cause or nature of A.J.K.'s acute event from October of 2014, and none of the details of the remaining medical records are necessary to understanding the expert opinions offered in this case. Of note, however, some further objective testing was performed during these later years.

On March 29, 2017, A.J.K. had a repeat EEG, with normal results. (*Id.* at 91.) However, the report indicates that "a normal interictal EEG does not necessarily exclude epilepsy." (*Id.*) A.J.K. was assessed with localization-related (focal) (partial) symptomatic and epileptic syndromes with complex partial seizures, not intractable, without status epilepticus. (*Id.*)

On October 22, 2017, A.J.K. had a repeat sleep study for concerns of obstructive sleep apnea. (*Id.* at 64-65.) There was no evidence of sleep apnea, but there was evidence of sleep deprivation. (*Id*.) On November 14, 2017, A.J.K. returned for further

evaluation at the allergy clinic. (*Id.* at 60.) Skin testing was performed and was negative with no evidence of an IgE reaction to her vaccines. (*Id*.) A.J.K.'s MMR and Hep A titers were positive, but her varicella titers was negative, meaning that A.J.K. was not protected in the event of exposure to varicella. (*Id*.) A.J.K.'s allergist recommended a varicella vaccination, but A.J.K.'s mother declined. (*Id*.)

On January 22, 2022, A.J.K. underwent a brain MRI with and without contrast, given her recurring seizures. (Ex. 226, p. 1.) The MRI revealed no acute intracranial abnormality or abnormal enhancement. (*Id*.) The radiologist recommended a comparison with prior imaging, but no further records were filed. (*Id*.) On January 25, 2022, A.J.K. underwent an EEG, which was abnormal for 1) bilateral independent focal epileptiform discharges seen in the occipital region and 2) right posterior quadrant slowing more prominently during hyperventilation. (Ex. 236, pp. 45-46.)

b. Danielle Kaltenmark's Testimony

On July 18, 2022, petitioners filed a declaration of Danielle Kaltenmark, A.J.K.'s mother. (Ex. 234.) She also testified during the hearing. (Tr. 6-63.) Mrs. Kaltenmark's testimony was largely consistent with her declaration. (*Id.*) During the hearing Mrs. Kaltenmark swore under oath and under the penalty of perjury that the contents of her declaration are true and correct to the best of her knowledge. (Tr. 62-63.)

Mrs. Kaltenmark describes A.J.K. as a "really happy baby" and "[s]he did not fuss much." (Ex. 234, p. 2.) Mrs. Kaltenmark explained that, during September of 2014, A.J.K. developed red spots on her skin and a fever "and she wanted to be held more." (*Id.*) Mrs. Kaltenmark suspected that A.J.K. had HFMD because it was making its way through her daycare group.[15] (*Id.*) Dr. Turner confirmed A.J.K. had HFMD, though Mrs. Kaltenmark declares that "she did not seem much bothered by the rash and she did well." (*Id.* at 3.)

On September 29, 2014, Mrs. Kaltenmark returned to Dr. Turner with A.J.K. for her 12-month well-visit. (*Id.*) A.J.K. "still had a bit of a rash from her [HFMD] but was otherwise doing well." (*Id.*) Mrs. Kaltenmark asked Dr. Turner if it was okay to proceed with A.J.K.'s vaccines since she had been sick recently, "but Dr. Turner assured [her] that A.J.K. would be fine." (*Id.*) A few months before this appointment, Mrs. Kaltenmark noticed that when A.J.K. was beginning to fall asleep, and sometimes in her sleep, "an arm or a leg would twitch." (*Id.*) These movements never happened when A.J.K. was wide awake, only when she was asleep or falling asleep. (*Id.*) Mrs. Kaltenmark describes "[w]hen it happened, her hand or foot wouldn't get stiff or anything, it was just a quick twitching movement, and it never seemed to wake her up or stop her from being able to fall asleep." (*Id.*) Mrs. Kaltenmark denies any conversation about seizure warnings or signs of seizures from this visit with Dr. Turner. (*Id.* at 4; *see also* Tr. 17-18.)

[15] Mrs. Kaltenmark was a medic in the Air Force at the time but was transitioning out of active service. (Ex. 234, p. 2.) She also worked at the same clinic as A.J.K.'s pediatricians Dr. Turner and Dr. Walker. (*Id.* at 2-3; Tr. 13.)

The next morning, Mrs. Kaltenmark describes waking up A.J.K., "which was unusual as she usually got up on her own, and she seemed out of it." (Ex. 234, p. 4.) She declares that A.J.K. was "twitching a lot even though she was awake, which was not normal, and [she] was just unfocused." (*Id.*) Mrs. Kaltenmark explains that A.J.K. threw up her milk when she fed her that morning. (*Id.*) When she took A.J.K. to see her father, they noticed that she was "beginning to jerk against her car seat restraint." (*Id.* at 4-5.) A.J.K. was awake at the time, and Mrs. Kaltenmark describes these movements as "totally different from the twitching we had seen as she was falling asleep." (*Id.* at 5.) Mrs. Kaltenmark decided to take A.J.K. to the emergency room. (*Id.*)

In the emergency room, A.J.K. began smacking her lips and her arm began shaking, and Mrs. Kaltenmark explained, "I had never seen her do anything like this before and I remember the nurse told me it looked like a seizure[.]" (Ex. 234, p. 5.) Thereafter A.J.K. underwent a lumbar puncture to rule out meningitis. (*Id.*) Petitioners were eventually sent home with a prescription for Keppra. (*Id.*) After returning home, Mrs. Kaltenmark declares that A.J.K. could not hold her bottle and, when Mrs. Kaltenmark lifted her arm, "it was just limp and dropped back down." (*Id.*) Mrs. Kaltenmark also describes how A.J.K. "tried to cry but it sounded more like a moan." (*Id.*) Petitioners returned to the emergency room, and later arranged to go to the Children's Hospital via ambulance. (*Id.* at 5-6.)

At the Children's Hospital, A.J.K. underwent testing, including brain imaging that revealed A.J.K. had had a stroke. (*Id.* at 6.) Mrs. Kaltenmark declares that "[t]hey did a lot of tests, but they could not find an obvious reason why she had the stroke." (*Id.*) Petitioners were directed to see a cardiologist and neurologist after A.J.K. was discharged. (*Id.*) A.J.K. ended up seeing a cardiologist "for a while and was on a medicine for hypertension for a short time." (*Id.*) However, A.J.K.'s physicians "ended up telling us that they did not think A.J.K. had high blood pressure at baseline and she was taken off the blood pressure medication without issue." (*Id.*)

After moving to Texas in 2015, petitioners brought A.J.K. to a neurologist who "told [petitioners] that he believes [A.J.K.'s] vaccinations triggered her condition." (*Id.*) Petitioners were informed about the Program and Mrs. Kaltenmark filed a VAERS report in 2015. (*Id.*) After A.J.K.'s vaccinations, she suffered physical effects from her stroke that required "intensive interventions, which lasted for years." (*Id.*) Mrs. Kaltenmark declares that A.J.K. participated in years of in-home physical, speech, and occupational therapy before starting outpatient visits. (*Id.*) Mrs. Kaltenmark notices some lingering effects and explains that A.J.K. will start additional speech therapy. (*Id.* at 6-7.) A.J.K.'s neurological injury also caused development delay, and Mrs. Kaltenmark explains that A.J.K. requires constant supervision. (*Id.* at 7.) Since her initial seizures and stroke in 2014, A.J.K remained on anti-seizure medication. (*Id.*) After almost two years without any seizure activity, A.J.K.'s seizures have returned in the last few years. (*Id.*)

Mrs. Kaltenmark also testified that there was no family history of stroke, despite Dr. Trasmonte's note indicating a "strong family history of stroke to the young." (*Id.* at 29, 47-48, 61-62 (citing Ex. 7, p. 25).)

V. Expert Opinions

a. Petitioner's experts

i. AHM Mahbubul Huq, M.B.B.S., Ph.D.[16]

1. *Diagnosis*

Dr. Huq opines that the most likely explanation for A.J.K.'s October 2014 presentation is PRES. (Ex. 24, p. 7; Tr. 84-86.) PRES is a clinical-radiological syndrome characterized by a variable combination of headaches, seizures, altered mental status, visual impairment, focal neurological signs and symmetric vasogenic edema in bilateral posterior cerebral circulation territory. (Zheng Chen et al., *Immune System Activation in the Pathogenesis of Posterior Reversible Encephalopathy Syndrome*, 131 BRAIN RSCH. BULL. 93, 93 (2017) (Ex. 47).) However, the symptoms and signs of PRES are not specific and can be seen in many other neurological disorders. (Jennifer E. Fugate & Alejandro A. Rabinstein, *Posterior Reversible Encephalopathy Syndrome: Clinical and Radiological Manifestations, Pathophysiology, and Outstanding Questions*, 14 LANCET NEUROLOGY 914, 918 (2015) (Ex. 68).) Brain imaging is therefore useful to exclude alternative diagnoses and usually confirms a diagnosis of PRES. (*Id.*) Brain imaging in cases of PRES generally reveals vasogenic edema in the parieto-occipital regions of both cerebral hemispheres. (*Id.*) The edema is typically asymmetric, but almost always bilateral. (*Id.*)

PRES is a relatively new diagnostic entity, though it is one that is increasingly recognized in clinical practice. (Tr. 70; Chen et al., *supra* Ex. 47, p. 93; Esther V. Hobson et al., *Posterior Reversible Encephalopathy Syndrome: A Truly Treatable Neurologic Illness*, 32 PERITONEAL DIALYSIS INT'L 590, 590 (2012) (Ex. 84)). However, PRES remains poorly understood. (*See Hobson et al.*, *supra* Ex. 84, p. 590.) Hobson et al. explain that PRES commonly evolves over a matter of hours, with the most common presenting symptoms being seizures, disturbed vision, headache, and altered mental state. (*Id.*) The severity of clinical symptoms varies, however. (*Id.*) Visual disturbances may manifest as blurred vision, homonymous hemianopsia, or even

[16] Dr. Huq was presented at hearing without objection as an expert in pediatric neurology and clinical genetics. (Tr. 71.) He received his medical degree from Dhaka Medical College in 1984. He is currently a professor of pediatrics and neurology at Wayne State University. (Ex. 25.) He was also the director of Children's Hospital of Michigan Gene Bank Research Facility from 2005-2013. (*Id.*) Dr. Huq has treated thousands of patients with epilepsy and developmental delay; and treats 20 to 25 patients each week with developmental delay. (Ex. 24.) He routinely manages cases of stroke and PRES while working in inpatient services at Children's Hospital of Michigan. (*Id.*) Dr. Huq has published peer reviewed articles on the genetics of epilepsy and various neurodevelopmental disorders, as well as a review article on pediatric stroke. (*Id.*; Ex. 25.)

cortical blindness. (*Id.*) Less common symptoms include nausea, vomiting, and brainstem deficits. (*Id.*) Hobson et al. indicate that seizures and status epilepticus are common, and nonconvulsive status epilepticus may be more frequent than generalized status epilepticus. (*Id.*) Signs of nonconvulsive seizures include stereotypic movements, such as staring, eye blinking, or head turning. (*Id.*)

PRES, Dr. Huq explains, is fundamentally a vascular disorder, "and, in this sense, very similar to stroke." (Ex. 24, p. 8.) Dr. Huq stresses that seizures occur in most patients with PRES, and status epilepticus occurs in approximately 13% of patients. (*Id.* (citing Fugate & Rabinstein, *supra,* at Ex. 68; Judy Hinchey et al., *A Reversible Posterior Leukoencephalopathy Syndrome,* 334(8) N. ENG. J. MED. 494 (1996) (Ex. 82)).) The disorder is typically associated with a number of complex clinical conditions, including preeclampsia / eclampsia, allogeneic bone marrow transplantation, solid organ transplantation, autoimmune diseases and high dose cancer chemotherapy. (*Id.* at 9 (citing W.S. Bartynski, *Posterior Reversible Encephalopathy Syndrome, Part 2: Controversies Surrounding Pathophysiology of Vasogenic Edema,* 29 AM. J. NEURORADIOLOGY 1043 (2008) (Ex. 37); Hobson et al., *supra* Ex. 84).) Although the incidence rate of PRES is unknown, Dr. Huq adds that nearly half of the patients with PRES have history of autoimmune disorder, "such as SLE, Rheumatoid arthritis, Sjogren's syndrome and Crohn's disease." (*Id.* (citing Fugate & Rabinstein, *supra* Ex. 68).)

Dr. Huq testified that A.J.K.'s brain MRI showed T2/FLAIR changes, which could be evidence of inflammation or vasogenic edema—meaning excessive water or edematous in the brain tissue. (Tr. 84.) In addition, A.J.K.'s MRI showed diffusion or restriction, indicating restricted water movement, which "can happen in ischemia or stroke but can also happen in other conditions such as PRES." (*Id.*) Dr. Huq opined that the MRI was consistent with PRES, rather than stroke, because bilateral occipital stroke "would be extremely uncommon, especially at this age." (*Id.*) According to Dr. Huq, bilateral occipital stroke usually occurs in older individuals. (*Id.*) Because the occipital lobe is supplied by the posterior cerebral artery, there would have to be a blocked clot in both the posterior cerebral artery on both sides, or a blocked clot or abnormality involving the basilar artery, which he opined is "really, really uncommon in a child." (*Id.* at 84-85.)

A.J.K.'s first treating neurologist, Dr. Trasmonte, had opined that, in PRES, the diffusion weighted images would show either equivocal findings or "if it is bright usually ADC mapping images would not be dark as seen in this patient." (Ex. 7, p. 2.) However, Dr. Huq disagrees. Dr. Huq testified that, in his clinical experience, the MRI images in PRES can be very variable, "and th[ese] particular findings are totally consistent with PRES." (Tr. 85-86.) Dr. Huq acknowledged that it can be difficult differentiating between cytotoxic edema and vasogenic edema. (*Id.* at 193-94.) However, he opined that, by looking at the apparent diffusion coefficient ("ADC") map, "you can confirm by the blackness of the ADC map. If the ADC map also show[s] blood, then you know it is actually the diffusion. It is not secondary signals that [are] coming from the T2 FLAIR signals." (*Id.* at 194.) Dr. Huq opined that the blackness on the ADC

does not differentiate between stroke and PRES, it simply rules out "T2 or FLAIR shine through." (*Id.*) He explained that it is a matter of degrees, and A.J.K.'s treating physician made a judgment call by "saying that it is too much diffusion restriction." (*Id.* at 195.)

Moreover, Dr. Huq explains that PRES is a misnomer, because while it's called "reversible" and "posterior," not all cases are reversible and not all cases are located in the posterior portion of the brain. (*Id.* at 86.) He estimates that 10 to 20 percent of cases turn out to be irreversible, where brain tissue is lost, similar to stroke; and PRES can also involve the frontal lobe, basal ganglia, and cerebellum. (*Id.*) Therefore, he maintains that petitioner's correct diagnosis is PRES, even though it proved not to be reversible, which was also later confirmed by A.J.K.'s treating neurologist Dr. Hsieh.[17] (Ex. 3, p. 241.) Furthermore, Dr. Huq stresses that nothing was found in terms of either a vascular abnormality, cardiac abnormality, or any blood clotting abnormality. (Tr. 90.)

During her inpatient stay, there was initial concern that A.J.K.'s blood pressures were high, prompting a consult from cardiology; however, Dr. Huq explains that her blood pressure levels were normal or borderline hypertensive. (*Id.* at 90-91 (citing Ex. 7, p. 64).) A.J.K.'s mean blood pressure was 77, and with this mean blood pressure, Dr. Huq opines that "the brain should have no problem having adequate blood supply, or . . . there would not be any fluctuation. [The b]rain would be able to autoregulate this kind of variation." (*Id.*) A.J.K.'s renal USG and cardiac echo were normal. (*Id.* at 91.) Dr. Huq explains that children who are hospitalized may become agitated and, as a result, the blood pressure measurement can be difficult. (*Id.*) He further notes that A.J.K.'s treating cardiologist opined that her blood pressure could have been secondary to the neurological involvement. (*Id.* at 92; Ex. 12, p. 7.)

Lastly, Dr. Huq testified that A.J.K.'s ongoing seizures could be caused by PRES, though he cannot be sure. (Tr. 99.) Simply put, "[n]othing is ever from one cause." (*Id.*) PRES, however, "would be enough to explain her clinical condition." (*Id.*)

2. Theory of causation

Dr. Huq opines that "vaccination and infection have worked synergistically to produce A.J.K.'s neurological illness." (Ex. 166, p. 1; *see also* Tr. 123-24.)[18] One

[17] Dr. Huq acknowledged that Dr. Hsieh's initial impression was that A.J.K. suffered from either a metabolic disease, such as mitochondrial disease, or PRES. (Ex. 3, p. 241.) However, whole exome and mitochondrial sequencing ruled out a metabolic or mitochondrial disorder. (Tr. 95.)

[18] During the hearing, Dr. Huq acknowledged that he misworded his earlier expert report wherein he stated that A.J.K. suffered a significant aggravation of her underlying condition. (Tr. 155 (citing Ex. 24, p. 6).) He acknowledged that A.J.K. suffered a "significant aggravation" from her previous condition—where she was a healthy child with some borderline concern on gross motor function and some muscle twitches. (*Id.*) Dr. Huq testified that he was "just comparing her pre-vaccination and post-vaccination condition, so it's probably not the appropriate choice of . . . word on [his] part." (*Id.* at 156.) There was no aggravation of an underlying condition because Dr. Huq "didn't think that [A.J.K.'s] muscle twitches [were] epilepsy." (*Id.*)

potential mechanism of "synergistic impact" occurs where there is a still unresolved infection, meaning there are activated immune cells or a low-level elevation of cytokines, in addition to vaccine-induced immune response. (Tr. 123-24.) Alternatively, the vaccination and the cytokine changes may disrupt the blood-brain barrier, resulting in increased entry of the virus into the brain tissue (an atypical presentation). (*Id*. at 124.)[19] The whole sequence of events, he testified, is triggered by endothelial wall injury. (*Id.* at 98.) There are various hypotheses for what causes the endothelial wall injury, but most agree that the blood vessels in the posterior part of the brain are more susceptible because there are less autoregulatory mechanisms available in the posterior circulation rather than in the anterior circulation. (*Id.*) Dr. Huq deferred to Dr. Gershwin regarding the role of cytokines in petitioners' theory. (*Id.* at 125.)

Dr. Huq explained that vasogenic edema results from increased permeability of capillary endothelial cells. (*Id.* at 99-100.) Endothelium and other cells surround the capillaries and the small arteries in the brain, creating a barrier between the blood and the brain tissue. (*Id.*) If the blood-brain barrier is impaired in any way, material from the blood, such as serum or the fluid from the blood (or even other molecules from the blood), extravasates into the brain tissue. (*Id.* at 100.) On objective testing, vasogenic edema presents as abnormality to FLAIR changes. (*Id.*) However, according to Dr. Huq, PRES may also present clinically with cytotoxic edema. (*Id.*) He explains that cytotoxic edema can "happen in metabolic causes . . . such as mitochondrial disorder or stroke, but it can also happen from PRES in 15 to 30 percent of cases." (*Id.*) In other words, one-fourth of cases of PRES will demonstrate diffusion restriction, like in petitioner's case.

Dr. Huq acknowledges that the exact mechanism of PRES is controversial, but endothelial dysfunction is suspected. (Ex. 24, p. 9 (citing Hobson et al., *supra* Ex. 84).) One commonly postulated theory is that severe hypertension causes interruption to brain autoregulation. (*Id.* (citing Bartynski, *supra* Ex. 37).) Bartynski explains that cerebral blood flow is usually regulated by dilatation and constriction of vessels to maintain adequate tissue perfusion, while simultaneously avoiding excessive intracerebral hypertension. (*Id.*) Uncontrolled hypertension leads to hyperperfusion and cerebral vessel damage, resulting in interstitial extravasation of proteins and fluids, causing vasogenic edema. (*Id.*) Dr. Huq emphasizes that conditions that commonly co-exist in PRES, such as chronic hypertension and atherosclerosis, are known to reduce the effectiveness of autoregulation. (*Id.*) However, the autoregulation theory does not explain (a) why blood pressure in PRES does not usually reach the upper limit of autoregulation, (b) why PRES often occurs in the absence of hypertension, or (c) why the extent of the edema is not directly related to the severity of the blood pressure. (*Id.* (citing Bartynski, *supra* Ex. 37; Alexander McKinney, *Posterior Reversible Encephalopathy Syndrome: Incidence of Atypical Regions of Involvement and Imaging Findings,* 189 AJR 904 (2007) (Ex. 96)).) Moreover, Dr. Huq testified that the hyperperfusion theory has never been documented, for example, on PET scan. (Tr. 103.)

[19] Dr. Huq clarified that a virus entering the brain was not required for his causal opinion. (Tr. 189.)

Dr. Huq suggested that evidence from some positron-emission tomography studies actually demonstrates cerebral hypoperfusion. (Ex. 24, p. 9 (citing Bartynski, *supra* Ex. 37).) He testified that hypoperfusion also causes restricted diffusion. (Tr. 104.) Without adequate metabolite, such as glucose or fatty acids or oxygen, not enough ATP is produced, which in turn restricts water molecule movement. (*Id.*) As it relates to this case, Dr. Huq testified that A.J.K. only demonstrated borderline hypertension and "it would be very hard to explain how that level of blood pressure would cause endothelial injury." (*Id.* at 107.)

Dr. Huq favors the cytokine theory because a vast majority of cases have some sort of autoimmune condition or immune-mediated condition. (*Id.* at 104.) In petitioner's case, Dr. Huq explained that, judging by the remnant of rash from her HFMD, there was some preceding "immune abnormality" occurring due to A.J.K.'s ongoing infection. (*Id.* at 113.) The cytokine or immune response from A.J.K.'s vaccination "could have been synergistic or additive in her case." (*Id.* at 113-14.) According to Dr. Huq, this is the mechanism that more likely than not caused the endothelial injury in A.J.K.'s case. (*Id.* at 114.)

On cross examination, Dr. Huq agreed that the Fugate paper he relied upon regarding cytokine-mediated PRES did not conclude that vaccines cause PRES. (*Id.* at 179.) Fugate et al. did observe that "[c]ytokine activation might also underlie the pathophysiological changes associated with both PRES and other systemic disorders, such as sepsis." Fugate & Robinson, *supra* Ex. 68, p. 4. However, Dr. Huq agreed that A.J.K. did not suffer from any systemic disorders. (Tr. 179-80.) Dr. Huq testified if A.J.K. had been suffering from SLE, for example, then he would assume that SLE were the cause of her PRES. (*Id.* at 180.) The reason Dr. Huq considered the vaccines and the "synergism between her infection" is because A.J.K. *did not* have any kind of underlying cause that would otherwise explain her PRES. (*Id.*)

3. *Logical Sequence of Cause and Effect*

Prior to the alleged vaccinations, Dr. Huq testified that A.J.K. was a healthy child, and she was developing normally. (*Id.* at 128.) There was some concern about borderline scores on her ASQ, but Dr. Huq stressed that on physician's direct exam, those concerns were not validated. (*Id.*) Based on his clinical experience, Dr. Huq testified that "these sort of borderline concerns often resolve unless you identify a significant genetic problem." (*Id.*) Upon receiving the four alleged vaccinations, Dr. Huq opines that there were "increased proinflammatory cytokine[s]" and "probably recruitment of the immune cells at that time." (*Id.*) He opines that A.J.K. possibly had somewhat elevated inflammation because of her still-recovering HFMD. (*Id.*) This led to an endothelial injury—and the endothelial dysfunction and blood-brain barrier disruption caused vasogenic edema, hypoperfusion, and energy failure, all leading to restricted diffusion and irreversible PRES. (*Id.* at 128-29.) Dr. Huq opines that this led to ongoing seizures during a critical period of development and, therefore, ultimately to

her current cognitive and developmental impairments as well as her uncontrolled epilepsy. (*Id*. at 129.)

At the hearing, I asked Dr. Huq whether A.J.K.'s ER records, which indicated that the CT scan showed pansinusitis and the x-ray showed a haziness in the lungs, had any bearing on A.J.K.'s resolving HFMD or whether it indicated another underlying infection was present. (*Id.* at 187.) Dr. Huq testified that these findings supported his theory that A.J.K.'s case was a "perfect storm." (*Id.*) Sinusitis is a localized infection, however, Dr. Huq explained that if there is inflammation going on in the sinus and immune cells, then there is probably an increase in inflammatory cytokines as well. (*Id.*) Sinusitis is a very common condition, and sinusitis alone would not be sufficient. (*Id.*) However, Dr. Huq suggested that A.J.K.'s pansinusitis could have been some viral pneumonia, which could have been another susceptibility factor. (*Id.* at 187-88.)

Dr. Huq opines that but-for the vaccinations, A.J.K. would not have developed PRES. (*Id.* at 197-98.) A.J.K. had ongoing sinusitis, and was recovering from HFMD, but he opines that the more acute, or direct, cause of immune activation and cytokine response were the alleged vaccinations. (*Id.* at 198.) Dr. Huq acknowledged that there is no "direct evidence" of excessive circulating cytokines because cytokine levels were not measured. (*Id*. at 177.) However, despite not having any "direct evidence" of elevated levels of cytokines, Dr. Huq testified that "we know the way that vaccine[s] work[] . . . . [b]oth the antigenic component and the adjuvant are recognized by the innate immune system, by the pattern recognition receptors, which include immune cells very early, almost immediately after giving the vaccines. And then they produce cytokines which are both local and distant . . . ." (*Id.* at 178.)

4. *Proximate temporal relationship*

Dr. Huq notes that A.J.K. developed a low-grade fever, clusters of seizures with status epilepticus, and a stroke-like episode vs PRES, within two days of administration of her MMR, Influenza, Hep A, and Varicella vaccines at 12 months of age. (Ex. 24, p. 16.) He opines that this timing is consistent with the proposed mechanism of inflammation, blood-brain barrier disruption, and release of cytokines by these vaccines. (*Id.*) As opposed to antibody production by B cells and memory cells, Dr. Huq opines that "inflammation after vaccination is an early event." (*Id.*) Given the role of inflammation and endothelial injury from proinflammatory cytokines, he suggests that a PRES or stroke-like event within days of vaccination is consistent with petitioners' proposed mechanism. (*Id.*)

According to Dr. Huq, epidemiological studies indicate that there are significantly elevated risks of febrile seizures 8 to 14 days after the receipt of MMR vaccine,[20] and an

[20] To support this assertion, Dr. Huq cites: Simon J. Hambidge et al., *Timely Versus Delayed Early Childhood Vaccination and Seizures,* 133 PEDIATRICS 1 (2014) (Ex. 75); Nicola P. Klein et al., *Measles-Mumps-Rubella-Varicella Combination Vaccine and the Risk of Febrile Seizures,* 126 Pediatrics 1 (2010) (Ex. 87); Nicola P. Klein et al., *Measles-Containing Vaccines and Febrile Seizures in Children Age 4 to 6 Years,* 129 PEDIATRICS 1 (2012) (Ex. 88); Nicola P. Klein et al., *Safety of Measles-Containing Vaccines in 1-Year-Old Children,* 135 PEDIATRICS 1 (2015) (Ex. 89); Kristine K. Macartney et al., *Febrile Seizures*

increased risk for febrile seizures during the 24 hours after a child receives the inactivated influenza vaccine at the same time as the pneumococcal 13-valent conjugate vaccine or the diphtheria, tetanus, acellular pertussis vaccine.[21] (*Id.*) As A.J.K. received both influenza and MMR vaccines, along with other vaccines, and developed a PRES or stroke-like episode, Dr. Huq opines that the timing of her seizures is consistent with proposed inflammatory mechanism, as well as epidemiological data. (*Id.* at 16-17.)

ii. M. Eric Gershwin, M.D., M.A.C.P., M.A.C.R.[22]

1. *Theory of Causation*

Dr. Gershwin first explained that the endothelial cells are part of the blood-brain barrier, which is, effectively, the barrier between the body and the brain. (Tr. 210.) The endothelial cells, are "not a cement wall," instead, they are "living tissue, and like any living tissue, fluid . . . and molecules can, in theory, go in both directions, go in and go out." (*Id.*) The release of cytokines, both proinflammatory and anti-inflammatory, is an expected event following vaccination. (*Id.* at 211.) Dr. Gershwin compared it to an infection, testifying that it is "not necessarily a pharmacologic burst with super-normal levels of cytokines [being] produced, but there are cytokines produced, and they do get in the blood, and [it is not] just the influence of the cytokines." (*Id.*) He explained that it is a "balance." (*Id.*)

Following Measles and Varicella Vaccines in Young Children in Australia, 33 VACCINE 1412 (2015) (Ex. 93); Shannon E. MacDonald et al., *Risk of Febrile Seizures After First Dose of Measles-Mumps-Rubella-Varicella Vaccine: A Population-Based Cohort Study,* 186 CMAJ 824 (2014) (Ex. 94); Margaret A. Maglione et al., *Safety of Vaccines Used for Routine Immunization of US Children: A Systematic Review,* 134 PEDIATRICS 325 (2014) (Ex. 95); Tania Schink et al., *Risk of Febrile Convulsions After MMRV Vaccination in Comparison to MMR or MMR+V Vaccination,* 32 Vaccine 645 (2014) (Ex. 106); Kumanan Wilson et al., *Adverse Events Following 12 and 18 Month Vaccinations: A Population-Based, Self-Controlled Case Series Analysis,* 6 PLOS ONE 1 (2011) (Ex. 126).

[21] Jonathan Duffy et al., *Febrile Seizure Risk After Vaccination in Children 6 to 23 Months*, 138 PEDIATRICS 1 (2016) (Ex. 63).

[22] Dr. Gershwin was presented at hearing without objection as an expert in immunology. (Tr. 207.) He received his bachelor's degree from Syracuse University in 1966, followed by his medical degree at Stanford University in 1971. (Ex. 232.) He then completed his internship and residency at Tufts-New England Medical Center in Boston, Massachusetts. (*Id.* at 2.) After completing a fellowship in immunology with the National Institutes of Health in Bethesda, Maryland, Dr. Gershwin became an Assistant Professor of Medicine (Rheumatology and Allergy) at the University of California School of Medicine in Davis, California ("UC Davis School of Medicine"). (*Id.*) Dr. Gershwin's medical licenses, with the exception of his California licensure, are currently inactive. (*Id.*) Dr. Gershwin has held a position at UC Davis School of Medicine for roughly 50 years. (Tr. 201.) He currently serves as a Distinguished Professor of Medicine in the Division of Rheumatology, Allergy and Clinical Immunology and the Director of the Allergy-Clinical Immunology program at UC Davis School of Medicine. (Ex. 232, p. 1.) Dr. Gershwin also currently serves as the Editor-in-Chief of the Journal of Autoimmunity, as well as several additional editorial positions for other publications focusing on autoimmunity. (*Id.* at 5.)

Upon vaccination, antigens will deposit in a local regional lymph node. (Tr. 212.) Dr. Gershwin testified that the antigens "activate the immune system" by first activating the innate immune system, alongside antibody or cytotoxic T cell production, and "in that process, cytokines are produced." (*Id.* at 212-13.) Cytokines travel in the blood, and "peak, in most cases within hours to a couple days at most." (*Id.* at 213.) This timeline varies by individual, specifically based on the genetics of the host, and depends upon the number of vaccines received. (*Id.*) The production of cytokines will ultimately lead to an adaptive response, the "protective response." (*Id.*) Dr. Gershwin explained that the levels of cytokines produced does not need to rise to the level of shaking, chills, or fever. (*Id.* at 214.) There must be a physiological alteration, as evidenced by endothelial cells affecting the tight junction of the blood-brain barrier. (*Id.*)

Dr. Gershwin stressed that this is "not an all-or-nothing process" or even a necessarily "pathologic injury." (*Id.* at 217.) In fact, there is "no necrosis[23] or death" taking place, which "is why measuring cytokines at any given moment is basically a law of diminishing returns." (*Id.*) He further explained, "We know they're there. The question is, when do you measure; do you measure in an hour; do you measure at four hours; where do you sample . . . . In a clinical setting, it's just very difficult to do within a patient." (*Id.*) He acknowledged that, "in all cases, if there's an effective immune response, there will be cytokine production." (*Id.* at 222.) However, quantifying what is an elevated response can be difficult. This is in part because "there is an enormous variation in the human response and genetic variation is expected." (Ex. 147, p. 2; *see also* Tr. 223.) And relatedly, there are "differences in cytokines that are produced by different individuals to different antigens." (Tr. 224.)

Responding to criticism from Dr. Forsthuber, Dr. Gershwin agreed that increased production of cytokines is an innate immune response that occurs post-vaccination and is arguably short-lived. (*Id.* at 233.) However, Dr. Gershwin stressed that "even if cytokines last in the blood a very short time, it's not how long they last in the blood," but "how long their biologic effect will last." (*Id.* at 232.) He explained that the role of cytokines in signaling and activating the immune process is what "becomes important," and even when cytokines levels are low, "the biologic response is significant." (*Id.* at 232-34.)

In A.J.K.'s case, Dr. Gershwin agreed that her HFMD virus was still a factor, even 13 days after her HFMD symptoms began and when A.J.K. was reportedly feeling a lot better. (*Id.* at 235.) He explained that her body was likely still in the process of "making a protective response, adaptive response," as such a process could take up to six weeks or longer. (*Id.*) He further testified that the vaccines alone could not have caused A.J.K.'s injury. (*Id.*) Instead, Dr. Gershwin supported Dr. Huq's synergistic theory, testifying that A.J.K had an ongoing viral infection, followed by an adaptive response, resulting in the release of cytokines where "the synergistic effect of the

[23] Necrosis is "the sum of the morphologic changes indicative of cell death and caused by the progressive degradative action of enzymes." *Necrosis*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=33333&searchterm=necrosis (last visited Oct. 25, 2023).

cytokine biology . . . is enough to open up the blood-brain barrier." (*Id.* at 237.) He went on to explain that this process "will activate either receptors on those endothelial cells" or "activate microglia themselves," and "[t]hey will themselves then produce additional cytokines which will further the inflammation." (*Id.)*

Dr. Gershwin acknowledged that "clinical evidence" from A.J.K.'s medical records does not exist to support his theory involving cytokines. (*Id.* at 262-63.) He candidly testified that, "if you're looking for a smoking gun within the clinical record, of course, you're not going to find it." (*Id.* at 263.) As explained by Dr. Huq, cytokines are difficult to measure. (*Id.* at 262.) According to Dr. Gershwin, cytokines are not very stable when they are removed from the blood. (*Id.*) This is why, as Dr. Huq indicated, cytokines are often measured by removing peripheral blood cells, stimulating them, and then measuring them—a process which is still fraught with difficulty. (*Id.* at 262-63.) Additionally, measuring ultrastructure on a microscope, or what the blood-brain barrier looked like in A.J.K., is not an available option. (*Id.* at 263.) Instead, Dr. Gershwin maintains his reliance on the clinical science, published in peer-reviewed literature, involving studies on the blood-brain barrier and cytokines. (*Id.*)

When I asked Dr. Gershwin whether the degree of effect on the endothelial cells, in terms of "opening or tightening the junction," correlates to the degree of the edema, Dr. Gershwin testified affirmatively. (*Id.* at 267.) He explained that there has to be a "significant disruption of the endothelial cells, because I don't think a minor disruption would make any difference." (*Id.*) Likewise, I asked Dr. Gershwin whether a similar correlation could be drawn between the degree of cytokine response and the degree to which endothelial junctions show dysfunction. (*Id.* at 267-68.) He testified that the magnitude of endothelial dysfunction may be a matter of the magnitude of the cytokine response; however, it may also be a matter of the relative levels of different cytokines because there is "a homeostasis involved with cytokines." (*See id.* at 268.) "[C]ytokines and their effect are modulated by each other," meaning that it is not as simple as identifying, for example, the "absolute level" of gamma interferon ("IFN") plus a level of interleukin-17.[24] (*Id.*) Cytokines involve regulation, so regulation or homeostasis may be disrupted. (*Id.*)

2. *Logical sequence of cause and effect*

Dr. Gershwin opined that A.J.K. had "an ongoing viral infection with an RNA virus,"[25] as evidenced by rash as well as "some evidence of an interstitial process . . . in the lung." (*Id.* at 239.) Therefore, in addition to a "multiplicity of innate cytokines being produced" as a result of A.J.K.'s vaccinations, cytokines were also being produced as part of the adaptive response to the virus. (*Id.* at 212, 239.) Cytokines likely altered the blood-brain barrier by interacting with the microglia to produce inflammation, resulting in edema in the brain. (*Id.* at 226, 240-41.) He opines that these were the inflammatory

[24] "Interleukin" is hereinafter abbreviated to "IL."

[25] In his expert report, Dr. Gershwin explains that HFMD is an RNA virus. (Ex. 147, p. 3.)

mediators that produced the swelling in A.J.K.'s brain, which led to what Dr. Huq defined as PRES. (*Id.* at 240-41; Ex. 147, p. 3.)

3. *Proximate temporal relationship*

Dr. Gershwin testified that the timing in A.J.K.'s case is "perfect for a first responder innate immune response, meaning this happened 48 hours later." (Tr. 240-41.) In response to Dr. Forsthuber's criticisms that the timing in this case is too short for petitioners' theory of causation, Dr. Gershwin agreed that it takes approximately three days for a T cell immune response to become detectable in regional lymph nodes. (Tr. 241.) However, Dr. Gershwin stresses that the adaptive response to HFMD includes "both T cells and antibody" and that T cells are not involved in this case. (*Id.* at 241-42.) Cytokines are produced as part of the innate immune response upon vaccination, and they have short half-lives of hours to a couple days. (*Id.* at 241.)

b. Respondent's experts

i. Thomas Gunter Forsthuber, M.D.[26]

Dr. Forsthuber stated that, in his initial understanding of the medical records, his impression was that A.J.K.'s clinicians thought that she more likely suffered a stroke. (Tr. 377.) However, during the hearing, he testified that "[f]rom the discussion that . . . we [have] had here over the last two days, I think now -- I believe more likely than not this to be PRES, which then evolved . . . into stroke. That would be my interpretation." (*Id.*)

Dr. Forsthuber opines that A.J.K.'s 12-month vaccinations did not cause PRES via immune activation and inflammation. (Ex. A, p. 8.) First, Dr. Forsthuber explains that the etiology of PRES is poorly understood, but two leading theories have emerged: 1) The "hyperperfusion theory," where a rapid increase in arterial blood pressure leads to cerebral hyperperfusion, vascular leakage, and vasogenic edema; and 2) the "toxic" theory, where endothelial dysfunction is caused by circulating endogenous or

[26] Dr. Forsthuber was presented at hearing without objection as an expert in immunology. (Tr. 321.) In 1987, he received his medical degree from University of Tübingen in Germany. (Ex. B.) He obtained his medical license in the United States in 1996. (*Id.* at 2.) Dr. Forsthuber maintained his medical license in Ohio until 2016 when it became voluntarily inactive. (*Id.*) He currently serves as a professor of immunology and the endowed chair of biotechnology at the University of Texas at San Antonio as well as an adjunct professor of pathology and of microbiology and immunology at the University of Texas Health Sciences Center in San Antonio, Texas. (*Id.*) He is board certified in anatomical and clinical pathology. (*Id.*) However, Dr. Forsthuber is not involved in active patient care, and he has not treated patients with A.J.K.'s clinical condition. (Ex. A, p. 1.) He defers to Dr. Bingham regarding the discussion of A.J.K.'s medical facts and clinical diagnosis. (*Id.* at 1, 3.) He has published "over 90 publications, reviews, and book chapters in the fields of T cell immunology and autoimmune diseases including multiple sclerosis and autoimmune diabetes (Type 1 diabetes) and their respective animal models." (*Id.* at 1.) Dr. Forsthuber is an editor / editorial board member of a number of journals, including Expert Reviews Clinical Immunology, Neurology: Neurology & Neuroinflammation, Journal of Immunology, and Frontiers in Multiple Sclerosis and Neuroimmunology. (*Id.*)

exogenous "toxins." (*Id.* (citing Marlene Fischer & Erich Schmutzhard, *Posterior Reversible Encephalopathy Syndrome,* 264 J. NEUROLOGY 1608 (2017) (Ex. 66; Ex. A, Tab 7).) The "toxic" theory proposes that endothelial cell dysfunction of arterial blood vessels in the brain is triggered by excessive release of proinflammatory cytokines or other inflammatory mediators, resulting in endothelial activation, release of vasoactive mediators, increased vascular permeability, and edema formation. (*Id.*) Regarding this theory, Dr. Forsthuber notes that nearly half of PRES patients have a history of conditions presenting with immune activation, such as autoimmune diseases and SLE, in particular. (*Id.* (citing Fischer & Schmutzhard, *supra* Ex. A, Tab 7).) Dr. Forsthuber stresses that vaccination has neither been established as a cause of PRES nor been discussed as relevant by researchers in this field. (*Id.*)

Dr. Forsthuber indicates that there are only two case reports of PRES temporally associated with vaccination, both after MMR vaccination. (*Id.* (citing Kursad Aydin et al., *Reversible Posterior Leukoencephalopathy and Adie's Pupil After Measles Vaccination,* 21 J. CHILD NEUROLOGY 525 (2005) (Ex. 34; Ex. A, Tab 8); Tadanori Hamano et al., *Posterior Reversible Encephalopathy Syndrome Following Measles Vaccination,* 298 J. NEUROLOGICAL SCIENCES 124 (2010) (Ex. 74; Ex. A, Tab 9)).) Importantly, Dr. Forsthuber indicates that onset of PRES in these reports was approximately 4-7 days after vaccination, which is significantly later than onset in the present case. (*Id.*) Aydin et al. reported a young male patient who was diagnosed with PRES ten days after receipt of a measles vaccination. (Tr. 329-30 (citing Aydin et al., *supra* Ex. A, Tab 8).) However, Dr. Forsthuber stressed that this case report is "really only a temporal association." (*Id.*) Dr. Forsthuber observes that this paper included neither an infectious inflammatory disease work-up nor a description of blood pressure changes. (*Id.*) He further notes that the child normalized one year later. (*Id.*) The second case report involved a 19-year-old student who was subsequently diagnosed with myeloradiculopathy with PRES following receipt of a measles vaccination. (*Id.* at 330 (citing Hamano et al., *supra* Ex. A, Tab 9).) In that case, Dr. Forsthuber stressed that the patient developed itching and pain hours after vaccination, which seemed to be progressive, but the PRES diagnosis was made approximately seven to ten days post-vaccination. (*Id.* at 331.) Although Dr. Forsthuber acknowledged that this patient did have elevated blood pressure, he again noted that this case report lacked both an infectious disease work-up and a causal theory, relying instead on a temporal association. (*Id.*)

Despite a surge of interest in PRES, he emphasizes that no additional case reports associating this condition with vaccination have emerged. (Ex. A, p. 8.) Instead, Dr. Forsthuber suggests that inflammatory conditions typically observed in the context of PRES are associated with striking systemic immune activation and/or immune dysregulation, such as SLE, eclampsia, transplantation, chemotherapy, or sepsis. (*Id.* (citing Fischer & Schmutzhard, *supra* Ex. A, Tab 7).) Infections associated with PRES are usually acute, systemic, and often chronic, such as immunocompromised patients with HIV or patients on immunosuppressive treatments after solid organ or bone marrow transplantation. (*Id.*) Dr. Forsthuber maintains that there is no evidence that A.J.K.'s vaccinations "resulted in the same level of immune

activation as the conditions typically associated with PRES." (*Id.*) Indeed, A.J.K. was afebrile (97.3° F body temperature) when she was first seen for seizures in the emergency department at South Georgia Medical Center. (*Id.* (citing Ex. 9, p. 56).) Moreover, no other adverse reactions were reported after her vaccinations on September 29, 2014. (*Id.*) According to Dr. Forsthuber, the lack of fever, or any other local or systemic signs, after vaccination undermines the theory of systemic elevation of proinflammatory cytokines, such as tumor necrosis factor ("TNF") or IL-6, as "fever typically rises in parallel with an increase in these cytokines." (*Id.* (citing A. Engel et al., *Kinetics and Correlation with Body Temperature of Circulating Interleukin-6, Interleukin-8, Tumor Necrosis Factor Alpha and Interleukin-1 Beta in Patients with Fever and Neutropenia,* 22 INFECTION 160 (1994) (Ex. A, Tab 10)).) Moreover, he testified that there were no laboratory abnormalities in A.J.K.'s CSF; that her blood labs, including her C-reactive protein ("CRP"), were normal; and that there was no report demonstrating any other abnormal results. (Tr. 323.) CRP, he explained, is a sensitive protein for inflammatory processes. (*Id.*) He opines that it is "highly unlikely" that A.J.K.'s vaccinations caused systemic immune activation and inflammation sufficient to trigger her neurological condition. (Ex. A, p. 8.)

Moreover, Dr. Forsthuber opines that there is no evidence of elevated levels of cytokines in HFMD patients. (Tr. 332-33.) He discussed a study that examined children in China with mild and severe HFMD, which concluded that there was no difference in cytokines (IL-1β, IL-6, or TNF) between children with mild HFMD and healthy controls. (*Id.* at 333 (citing Kang Cai et al., *Clinical Characteristics and Managements of Severe Hand, Foot and Mouth Disease Caused by Enterovirus A71 and Coxsackievirus A16 in Shanghai, China*, 19 BMC INFECTIOUS DISEASES 1 (2019) (Ex. J)).) He stressed that this study showed no elevation in CRP among the mild HFMD patients. (*Id.*) Dr. Forsthuber testified that CRP is tightly linked to IL-6 as CRP is induced by IL-6 in the liver. (*Id.* at 334.) He explained that IL-6 levels rise first, and then approximately 19 to 20 hours later, CRP levels go up. (*Id.*)

Dr. Forsthuber opines that there is a "huge distinction" between cytokine levels in the blood and "levels of cytokines produced by peripheral blood mononuclear cells isolated from the blood." (*Id.* at 336.) He explained that, while vaccines clearly induce an immune response by way of T cell and antibody responses, there is no literature to support the theory that vaccines induce levels of cytokines that have a meaningful effect in the blood. (*Id.* at 336-37.) He pointed to several articles concluding that "the levels of cytokines in the blood, in serum or plasma, induced after vaccination are slight and short-lived." (*Id.* at 337 (citing Caroline Herve et al., *The How's and What's of Vaccine Reactogenicity*, NPJ VACCINE, Sept. 24, 2019 (Ex. 182)).) Dr. Forsthuber opines that these slight levels of cytokines induced by vaccination cannot play a role. (*Id.*) According to Dr. Forsthuber, Kleiner et al. "clearly shows that you can detect most cytokines in the serum of healthy patients." (*Id.* at 338 (citing Giulio Kleiner et al., *Cytokine Levels in the Serum of Healthy* Subjects, MEDIATORS OF INFLAMMATION, Mar. 2, 2013 (Ex. E, Tab 17)).) He explained that the healthy individuals in this study all had a certain level of IL-6 and TNF in their blood. (*Id.*) He noted that Kleiner et al. is not the only study finding baseline levels of proinflammatory cytokines in the blood of

individuals. (*Id.* at 338.) Regarding the *level* of cytokines, Dr. Forsthuber testified that Kleiner et al. reported levels of cytokines in picograms—a picogram amounts to one trillionth of a gram. (*Id.* at 338-39.)

Dr. Gershwin cites several sources to support his assertion that vaccines induce cytokines that have a clinically dramatic impact on the body. (Ex. 147, p. 2 (citing Joan E. Nichols et al., *Human Macrophage Responses to Vaccine Strains of Influenza Virus: Synthesis of Viral Proteins, Interleukin-1β, Interleukin-1, Tumour Necrosis Factor-α and Interleukin-1 Inhibitor*, 11 VACCINE 36 (1993) (Ex. 148); Juliana Gil Melgaço et al., *A Single Dose of Inactivated Hepatitis A Vaccine Promotes HAV-Specific Memory Cellular Response Similar to that Induced by a Natural Infection*, 33 VACCINE 3813 (2015) (Ex. 149); Stephen C. De Rosa et al., *Vaccination in Humans Generates Broad T Cell Cytokine Responses*, 173 J. IMMUNOLOGY 5372 (2004) (Ex. 150); Jennifer P. Wang et al., *Varicella-Zoster Virus Activates Inflammatory Cytokines in Human Monocytes and Macrophages Via Toll-Life Receptor 2*, 79 J. VIROLOGY 12658 (2005) (Ex. 151); Herve et al., *supra* Ex. 182).) Dr. Forsthuber, however, testified that all of these papers examined cytokine production in tissue culture. (Tr. 343.) According to Dr. Forsthuber, these studies are isolating monocytes from the blood, putting them in culture, and then exposing them to a virus. (*Id.*) While these studies recorded high levels of cytokines, Dr. Forsthuber explained that, in these studies, the cells are stimulated in culture and "[i]f they don't stimulate the cells, they don't get any response." (*Id.* at 343-44.) Moreover, Dr. Forsthuber noted that there is a lot of information missing from these studies, such as how many cells are put in culture. (*Id.*) He opines that none of these studies have "anything to do with what's happening in the blood after vaccination." (Tr. 343-46.)

Dr. Forsthuber cites Christian et al., a study in which investigators looked at subjective side effects and proinflammatory cytokine responses in young women after influenza vaccination. (*Id.* at 347 (citing Lia M. Christian et al., *Proinflammatory Cytokine Responses Correspond with Subjective Side Effects After Influenza Virus Vaccination*, 33 VACCINE 3360 (2015) (Ex. E, Tab 15)).) Dr. Forsthuber highlighted Figure 1, which shows the amount of cytokines in picograms per milliliter. (*Id*. at 347-48.) Upon his review of the illustration in Figure 1, Dr. Forsthuber testified that he could not see any increase, much less a meaningful increase, in cytokines. (*Id.*) Moreover, Dr. Forsthuber relies on the study by Kashiwagi et al. (*Id.* at 349-50 (citing Yasuyo Kashiwagi et al., *Production of Inflammatory Cytokines in Response to Diphtheria-Pertussis-Tetanus (DPT),* Haemophilus Influenzae *Type B (Hib), and 7-valent Pneumococcal (PCV7) Vaccines*, 10 HUMANS VACCINES & IMMUNOTHERAPEUTICS 677 (2014) (Ex. E, Tab 16)).) Although Kashiwagi et al. observed "no association" between different vaccines and "stroke or fever," Dr. Forsthuber acknowledges that the study did not look at the vaccines in A.J.K.'s case, "so we can't really draw conclusions from this" regarding "the vaccines that are allegedly playing a role in our case." (*Id.* at 350.) Looking at the figures in the Kashiwagi et al. study, Dr. Forsthuber testified that the results showed increased cytokines among the *stimulated* PMBCs. (*Id.* at 351-53.) He noted that the cytokine levels were not notably higher 24 hours post-vaccination. (*Id*.) Dr. Forsthuber suggested, in line with Herve et al. cited by Dr. Gershwin, that Kashiwagi

et al. supports a finding that vaccines induced "very slight changes in cytokines, and they're very short-lived." (*Id.* at 353.)

Dr. Forsthuber acknowledged that the concept of cytokines acting in the blood-brain barrier is "a valid concept." (*Id.* at 354.) However, the level of cytokines required to make the blood-brain barrier permeable is an open question. (*Id.* at 354-55.) Dr. Forsthuber points to a study by de Vries et al., which investigated the effect of TNF, IL-1β, and IL-6 on the transendothelial electric resistance ("TEER") of endothelial cells, which was used as a model for the blood-brain barrier permeability. (*Id.* at 355 (citing Helga E. de Vries, *The Influence of Cytokines on the Integrity of the Blood-Brain Barrier In Vitro*, 64 J. NEUROIMMUNOLOGY 37 (1996) (Ex. 168)).) The authors sought to examine whether cytokines can induce changes in the blood-brain barrier in vitro. (*See* de Vries et al., *supra* Ex. 168, p. 38.) The results of the study demonstrated that cytokines induce a disruption of the blood-brain barrier at the level of the cerebral endothelial cells, which is evidenced by a decline in TEER. (*Id.* at 41.) However, Dr. Forsthuber testified that, in order to see these results, investigators had to "throw thousands to 50,000-fold higher concentrations on these cells in order to see a change in the permeability of the blood-brain barrier." (Tr. 356-57.) Dr. Forsthuber cautions that, from this study, we "[p]robably" cannot draw conclusions regarding "exactly what happens in people." (*Id.* at 357.) He suggests, instead, that we can conclude that slight increases in cytokines, induced after vaccination, will not change the blood-brain barrier. (*Id.* at 358.)

Dr. Forsthuber explained that cytokines in general have a "very short life span." (*Id.* at 360-61.) The half-life of most cytokines "ranges in the amount of minutes," although IL-6 has a somewhat longer half-life of about 16 hours. (*Id.* at 361.) Dr. Forsthuber stressed that when a cytokine is produced somewhere, it does not go into the bloodstream and remain there permanently—instead, cytokines quickly disappear. (*Id.*)

On cross-examination, Dr. Forsthuber provided two examples of contexts in which he agrees that cytokines act on the blood-brain barrier, causing injury. (*Id.* at 388.) First, he testified that injection of high levels of cytokines, or a substance that induces high cytokine levels, into an experimental animal or human, would presumably be injurious. (*Id.*) For example, he suggested that injury is "absolutely possible" after injection of high doses of lipopolysaccharide injected in an animal model. (*Id.*) Second, he testified that individuals with particular infections, such as sepsis or pneumonia, already have elevated cytokines in their blood. (*Id.* at 388-89.) In sepsis specifically, Dr. Forsthuber explained that there is often disseminated intravascular coagulation, "which is essentially a stroke formation all over the place, where cytokines can contribute." (*Id.* at 389.) These circumstances can likely lead to increased permeability in the blood-brain barrier by way of injurious cytokine levels, but the "level of cytokines is fairly high." (*Id.*) Dr. Forsthuber testified that we have "infections all the time," and yet, it is unclear "why, for example, an infection, upper respiratory or GI tract type infection . . . in the week preceding a stroke . . . increase the risk." (*Id.* at 389-90.)

Dr. Forsthuber opines that there is no logical sequence of cause and effect between A.J.K.'s vaccination and her injury on October 1st. (*Id.* at 369.) He stresses that there is no evidence that A.J.K. developed a systemic inflammatory response following the subject vaccinations. (*Id.*) On the contrary, Dr. Forsthuber testified that there is "clear evidence" against it, noting that A.J.K.'s CRP was normal. (*Id.*)

Dr. Forsthuber opines that the temporal relationship between A.J.K.'s vaccines and her injury that is drawn by petitioners is not medically appropriate. (*Id.* at 369-70.) He testified that adverse reactions, if they occur, are typically observed approximately 7 to 10 days after MMR and varicella vaccinations. (*Id.* at 370.) He further asserted that, in the two case reports of PRES following measles vaccination, onset was 10 days after vaccination in one case, and 4 to 10 days after vaccination in the other case. (*Id.*) Regarding the flu vaccine, Dr. Forsthuber observed that the majority of adverse reactions, including mild fever or body aches, occur within 24 hours post-vaccination. (*Id.* at 370-71 (citing Christian et al., *supra* Ex. E, Tab 15.).) Lastly, he testified that he was "not 100 percent sure about what the peak is for the hepatitis A vaccine," but he suggested that adverse reactions to adjuvanted vaccines generally occur during the first 24 hours. (*Id.* at 371.)

Lastly, Dr. Forsthuber is not convinced that A.J.K. had active HFMD at the time of her vaccinations. (*Id.* at 366.) He testified that "the rash is only infectious . . . while it's blistering, while there are live blisters." (*Id.*) He explained that a rash, in and of itself, does not evidence an active immune process. (*Id.* at 387.) Unlike in vasculitis, where a rash can indicate an immune reaction, HFMD involves viral rashes. (*Id.*) Dr. Forsthuber testified that "obviously [A.J.K.] had an infection, so her immune response is still ongoing. She will have . . . antibody production at that time. She will have lymphocytes that are primed and reactive against the measles vaccine and virus, and they will circulate in her body." (*Id.*) Without reencountering the virus, however, Dr. Forsthuber testified that they will not be reactivated. (*Id.*)

ii. Peter Bingham, M.D.[27]

Dr. Bingham opines that there is no evidence of brain inflammation in A.J.K.'s records. (Ex. C, p. 6.) Therefore, the relevance of the inflammatory mediators described in Dr. Huq's report is unclear since there was never any objective evidence of brain inflammation in this case. (*Id.* (citing Ex. 24, p. 14).) Dr. Bingham observes that

[27] Dr. Bingham was presented at hearing without objection as an expert in pediatric neurology. (Tr. 276.) He received his medical degree from Columbia College of Physicians & Surgeons in 1987. (Ex. D, p. 1.) He is a board-certified pediatric neurologist. (Ex. C, p.1.) He completed his residency in pediatric neurology and his fellowship training in neuromuscular diseases at The Children's Hospital of Philadelphia. (*Id.*) He has twenty-five years post-graduate experience as a clinician in general child neurology. (*Id.*) Dr. Bingham has published over thirty peer-reviewed medical articles. (Ex. D, pp. 3-6.) He has also written or co-authored all or parts of more than ten textbooks concerning neurology or pediatrics. (*Id.* at 6-7.) Presently, he serves as a professor of neurology and pediatrics at the University of Vermont. (*Id.* at 1.) He also serves as the staff physician (pediatric neurology) at Fletched Allen Health Care / University of Vermont in Burlington, Vermont. (*Id.* at 2.)

A.J.K. "had normal spinal fluid, and no suggestive signs of brain inflammation in terms of pattern of signal change on brain imaging (MRI) studies." (*Id.* at 6-7.) Moreover, he hypothesizes that, if there was brain inflammation, Dr. Huq should not have disregarded the possibility that a recent infection that A.J.K. experienced two weeks before her acute neurological illness, rather than vaccination, may have triggered either a brain vasculitis or vasculopathy, or a systemic hypercoagulable state mediated by inflammation. (*Id.* at 7.) Dr. Bingham suggests that an antecedent viral infection, such as A.J.K.'s HFM infection two weeks before she presented for stroke, may be an important etiological factor in pediatric stroke. (*Id.* (citing Heather J. Fullerton et al., *Infection, Vaccination, and Childhood Arterial Ischemic Stroke*, 85 NEUROLOGY 1459 (2015) (Ex. A, Tab 4; also filed as Ex. E, Tab 2)).) He further notes one particular virus—enteroviral infection, such as coxsackie viral infection—that may underlie HFMD has been associated with cerebral stroke. (*Id.* at 7, 10.)

Dr. Bingham also observes that A.J.K. did not present with a fever on the first trip to the emergency room on October 1, 2014. (Tr. 280-81.) Additionally, he testified that A.J.K. was hypertensive during her hospitalization in Georgia. (*Id.* at 285.) He observed A.J.K.'s systolic blood pressure at 141, which may not appear to be very high for an adult but "is a significant elevation for a 12-month-old." (*Id.*) Dr. Bingham opined that this was "severe hypertension." (*Id.*) He testified that anything above a 101 would put her, approximately, in the 99th percentile for systolic blood pressure for 12-month-old infants. (*Id.*) Based on the medical records and Mrs. Kaltenmark's testimony, Dr. Bingham suggested that A.J.K. had a relatively high body mass index, which can be associated with higher blood pressure in infants. (*Id.* at 285-86.) Moreover, he noted that A.J.K. was prescribed lisinopril to treat her high blood pressure. (*Id.* at 286.)

Dr. Bingham agrees that "the bilateral nature and absence of thrombus suggests the possibility of PRES." (Ex. C, p. 7.) He agreed on cross-examination that A.J.K.'s MRI from October 2, 2014, could also be consistent with PRES. (Tr. 299.) Specifically, he testified that the MRI are consistent with a "hint of a[n] atypical pattern of signal change." However, he indicated that the "test of time" is the distinguishing factor. (*Id.*) Dr. Bingham opines that "[t]he notion of reversibility reflects the problematic nature of this acronymic syndrome" because it may arise in diverse settings, *e.g.*, medication-induced and hypertension, that may prove *not* to be reversible. (Ex. C, p. 7.) In contrast to petitioners' experts, Dr. Bingham described PRES as an "evanescent diagnosis." (Tr. 290.) Dr. Bingham testified that his cited literature suggests that "if it doesn't reverse, then in the end, that would [be] a criterion that should be fulfilled if we are to call it PRES in the final analysis, if it proves not to be reversible." (*Id.* at 291.) "Particularly in the setting of hypertension, the occurrence of lasting encephalomalacic lesions—such as bioccipital stroke as identified in this case on follow-up MRIs of the brain—belies the assertion of reversibility in PRES." (*Id.*) In this case, he indicates that the bilateral lesions are most likely due to hypertension, which is perhaps the most commonly identified etiology of PRES. (*Id.*) This is presumably why A.J.K.'s treating physicians speculated that the neurological diagnosis could relate to severe hypertension. (*Id.*) Dr. Bingham emphasizes that PRES, as a neuroradiological syndrome, may have multiple possible underlying causes and that its pathogenesis is

not entirely clear. (*Id.*) However, he agrees with Dr. Huq that genetic or metabolic disorders seem unlikely considering all the findings taken together. (*Id.*)

Instead, Dr. Bingham testified that petitioner most likely suffered a stroke due to high blood pressure, in the context of a recent infection (HFMD). (Tr. 288; Ex. C, p. 8.) He opines, "[e]ven if the initial neuroradiological diagnosis was PRES, A.J.K.'s course reveals the problematic nature of this diagnosis in general, because of the irreversibility of her (occipital) brain injury." (Ex. C, p. 8.) With his clinical experience, Dr. Bingham recognizes the ambiguity regarding reversibility in the literature on PRES. (*Id.*) He explains that he would tend to put aside the "PRES" rubric and would describe the brain injury as a stroke. (*Id.*) Regardless of terminology, he opines that the brain injury evidently occurred no later than 2 days after she received her vaccinations on September 29, 2014, and "possibly before vaccination, as her clinicians speculated." (*Id.*) Dr. Bingham insists that "[t]here is no evidence from brain imaging or spinal fluid analysis that this brain pathology was inflammatory in nature." (*Id.*) He concludes that brain lesions seen on A.J.K.'s MRI were most likely due to the hypertension that was "presumably fluctuating in its course" because hypertension was not identified in notes reviewed at her initial presentation on October 1, 2014. (*Id.*) Dr. Bingham explains that hypertension is recognized as "one of the most common underlying causes" of PRES. (*Id.* at 10 (citing Thomas G. Liman et al., *Posterior Reversible Encephalopathy Syndrome*, 32 CURRENT OP. NEUROLOGY 25 (2019) (Ex. C, Tab 4)).) Relying on the fact that severe hypertension is a prominently identified cause of the neuroradiological abnormalities seen on A.J.K.'s MRI and that severe hypertension was documented within days of her presentation, Dr. Bingham opines that it is more "likely that hypertension contributed significantly to, and may have been the primary underlying cause of, her condition." (*Id.*) He explained that, despite both diagnostic terms being appropriate in this case, "the ultimate *irreversibility* of the occipital lesions on MRI belie the semantic implication of the acronym PRES." (*Id.*) Thus, Dr. Bingham indicates that stroke is a "more relevant and accurate description" of A.J.K.'s brain disease. (*Id.*)

However, Dr. Bingham agreed that a neurological injury similar to what A.J.K. experienced can itself cause hypertension or variable blood pressure. (Tr. 301.) He explained that higher "intracranial pressure and/or ischemic changes of the brain" can result in "a reactive elevation of blood pressure." (*Id.*) Though Dr. Bingham agreed that external factors, such as agitation, can influence blood pressure, he opined that treating A.J.K. for hypertension if her elevated blood pressure was an "artifact of agitation" would have been a mistake. (*Id.* at 301-02.) He subsequently agreed that A.J.K. was never treated for hypertension during her initial hospitalization and that A.J.K.'s treating cardiologists dismissed hypertension in her diagnoses. (*Id.* at 302-04 (citing Ex. 7, p. 25 ("Cardiology was consulted and they agreed that she is not hypertensive.")).)

Dr. Bingham testified that petitioners' theory of causation is unreliable because there is no "detailed pathophysiological data in this or any other published case report." (*Id.* at 293.) He further observed the lack of epidemiological evidence establishing vaccine-causation of PRES or pediatric stroke. (*Id.*) Contrary to Dr. Huq's assertion, Dr. Bingham stresses that Bartynski et al. does not present evidence that "PRES is

usually associated with a systemic inflammatory process." (Ex. C, p. 9 (quoting Ex. 24, p. 10.).) He stresses that "[t]his reference is problematic because it nowhere presents a concise or rigorous neuroradiological definition of PRES." (*Id.*) Dr. Huq refers to reports of patients with "febrile seizures and antibody mediated autoimmune encephalitis" in order to underline the importance of immune activation and seizures. (Ex. 24, p. 12.) However, Dr. Bingham stresses that the term "febrile seizures" should not be used in the setting of encephalitis. (Ex. C, p. 9.) "Furthermore, a response to ACTH or corticosteroids does not prove that the epilepsy is necessarily mediated by inflammation, since both of these compounds have effects on the nervous system that don't relate to neuronal inflammation per se." (*Id.*) Dr. Bingham could not say whether cytokines play a role in the pathogenesis of PRES. (Tr. 301.) He explained that it would be difficult to opine on the role of cytokines because they are not measured in clinical cases. (*Id*.) He further explained that it would be especially difficult to opine on the role of cytokines in cases where there is no hypertension. (*Id.*)

Related to timing, Dr. Bingham insists that Dr. Trasmonte's note (Ex. 7, p. 25) would have put the timing of these first seizures to the day of vaccination (September 29, 2014) or the day after (September 30, 2014). (Ex. C, p. 9.) "Using the standard for timing of dys-immune or inflammation-mediated adverse effects of vaccinations" from the Institute of Medicine, he opines that "even 2 days," *i.e.*, from when A.J.K. received the vaccination on September 29th to October 1st, seems to be "too short to accept as a likely timing interval." (*Id.*) Dr. Huq cites reports purportedly linking vaccination to seizures "8 to 14 days" after MMR vaccination. (Ex. 24, p. 16.) Dr. Bingham acknowledges that one reference suggests increase in seizures within 24 hours after influenza vaccination. (Ex. C, p. 9 (citing Duffy et al., *supra* Ex. 63.).) However, he stresses that A.J.K. "likely suffered neurodevelopmental consequences of her acute illness" with the MRI changes on or about October 1, 2014. (*Id.*)

Based on the timing and absence of evidence of brain inflammation in this case, as well as the absence of epidemiological evidence linking vaccination to pediatric stroke or PRES, Dr. Bingham opines that there is no logical sequence of cause and effect linking A.J.K.'s vaccination to her stroke or PRES. (*Id.* at 10.) Moreover, he stresses that none of A.J.K.'s treating physicians endorsed the idea that her brain pathology, as seen on MRI, was caused by her vaccinations. (*Id.*)

Dr. Bingham identifies two non-vaccine potential causes of A.J.K.'s stroke. (*Id.*) First, he opines that her hypertension could have caused her stroke. (*Id.*) Because A.J.K. had a normal blood pressure (100/52) during her transport on October 1, 2014, Dr. Bingham suggests that she had a "volatile hypertension" during this time. (*Id.* (citing Ex. 9, p. 42.)) He acknowledges, however, that the "ultimate cause" of A.J.K.'s hypertension "remains unknown." (*Id.*) Second, Dr. Bingham opines that A.J.K.'s antecedent systemic infection could have caused her stroke. (*Id.*) A.J.K. was diagnosed with HFMD, which is most commonly understood to be caused by enteroviral infection (*e.g.*, coxsackie infection). (*Id.*) Considering the evidence of enteroviral nucleic acid in the spinal fluid, Dr. Bingham cites a case report by Piccolo et al., but he cautions that it is not proven that A.J.K. had enteroviral infection. (*Id.* (citing Benedetta

Piccolo et al., *Transient Posterior Cerebral Arteriopathy: An Unusual Case Enterovirus-Related,* 21 BRAIN & DEV. 214 (2019) (Ex. C, Tab 1)).) Moreover, he stresses that "experts have noted that antecedent viral infection may be an important etiological factor in pediatric stroke." (*Id.* (citing Fullerton et al., *supra* Ex. C, Tab 2.)) When I asked Dr. Bingham about the likely mechanism by which infection could contribute to stroke, he testified that the "mechanism in any individual case is often without any kind of clear data," except that there is evidence of an effect on the clotting cascade in the case of a thrombotic stroke. (*Id.* at 309.) In A.J.K.'s case, however, Dr. Bingham noted that there is no evidence of clotting. (*Id.*)

VI. Discussion

Under the three-part *Althen* test, petitioners must demonstrate both that the vaccine(s) at issue "can" and "did" cause the alleged injury. *E.g.*, *Pafford v. Sec'y of Health & Human Servs*., 451 F.3d 1352, 1355-56 (Fed. Cir. 2006) (approving the special master's querying under *Althen* regarding, first, whether the vaccine "can cause" the alleged injury and, second, whether it "actually caused" the injury in the particular case). Whether a vaccine can cause the injury is addressed by petitioners' medical theory presented under *Althen* prong one. Even if the vaccines can cause the injury as a general matter, they must also demonstrate that the vaccines did cause the injury in this specific case. This is addressed under *Althen* prongs two and three, with prong three examining the timing of onset relative to vaccination and prong two examining whether a logical sequence of cause and effect implicates the vaccine(s) as causal.

In this case, I have determined that petitioners have not met their burden of proof under *Althen* prong one. Accordingly, because there is not preponderant evidence that vaccines can cause PRES, petitioners necessarily cannot demonstrate that they did *so* in this case. Therefore, *Althen* prongs two and three are addressed only in the interest of completeness. There is preponderant evidence under *Althen* prong three that the timing of onset could be appropriate for what petitioners theorize; however, timing alone does not support causation-in-fact. Even after resolving some of the factual disputes regarding A.J.K.'s medical history in petitioners' favor under *Althen* prong two, the limitations of the available clinical evidence still indicate that her condition is best viewed as idiopathic, regardless of whether it is viewed as stroke or PRES.

a. *Althen* prong one

Under *Althen* prong one, petitioner must provide a "reputable medical theory," demonstrating that the vaccine received can cause the type of injury alleged. *Pafford*, 451 F.3d at 1355-56 (quoting *Pafford v. Sec'y of Health & Human Servs.*, No. 01-0165V, 2004 WL 1717359, at *4 (Fed. Cl. Spec. Mstr. July 16, 2004)). Such a theory must only be "legally probable, not medically or scientifically certain." *Knudsen v. Sec'y of Health & Human Servs*., 35 F.3d 543, 548-49 (Fed. Cir. 1994). Petitioner may satisfy the first *Althen* prong without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. *See Andreu ex rel. Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1378-79

(Fed. Cir. 2009) (citing *Capizzano v. Sec'y of Health & Human Servs.,* 440 F.3d 1317, 1325-26 (Fed. Cir. 2006)). However, "[a] petitioner must provide a 'reputable medical or scientific explanation' for [her] theory. While it does not require medical or scientific certainty, it must still be 'sound and reliable.'" *Boatmon v. Sec'y of Health & Human Servs.*, 941 F.3d 1351, 1359 (Fed. Cir. 2019) (quoting *Knudsen*, 35 F.3d at 548-49).

The parties' differences regarding diagnosis are addressed separately under *Althen* prong two. For purposes of the discussion of *Althen* prong one, this section will focus on posterior reversible encephalopathy syndrome ("PRES"), which is the diagnosis preferred by petitioners' neurology expert, Dr. Huq. Even though Dr. Huq leaves open the possibility that A.J.K. ultimately suffered a stroke, he opines that the stroke, if it occurred, would have occurred in the context of PRES. (Ex. 133, p. 1.) Despite extensive discussion of stroke in this case, petitioners have not ultimately relied on any theory of vaccine causation that does not involve the vaccinations at issue having been a substantial contributing factor to PRES.[28]

Two considerations are addressed in turn – (1) whether PRES is recognized as a cytokine-mediated condition such that petitioners' theory would even have the potential to be possible, and (2) if so, whether vaccinations in particular can be implicated as a cause of PRES. For the reasons discussed below, I conclude that petitioners have preponderantly established the first point, but not the second. This conclusion should not necessarily be surprising. There is very little by way of prior analysis by other special masters regarding PRES specifically. However, many cases in the Program have sought to prove, in a variety of contexts, that a post-vaccination cytokine response can disrupt the blood-brain barrier and lead to injury to the central nervous system. These cases have often, though not uniformly, failed with respect to *Althen* prong one. *See, e.g.*, *Castaneda ex rel. N.A.C. v. Sec'y of Health & Human Servs*., No. 15-1066V, 2020 WL 3833076, at *23-27 (Fed. Cl. Spec. Mstr. May 18, 2020) (rejecting a theory that vaccination can cause pediatric acute onset neuropsychiatric syndrome (PANS) because, though inflammation is hypothesized as a cause of PANS and vaccines produce cytokines, "petitioner has not presented evidence through her expert or through literature as to the level of that production, or what level is required to be pathologic"), *review denied,* 152 Fed. Cl. 576 (2020); *Martin v. Sec'y of Health & Human Servs*., No. 15-789, 2020 WL 4197748, at *30 (Fed. Cl. Spec. Mstr. May 8, 2020) (explaining in a case of SIDS that "[p]etitioners' experts did not persuasively establish that cytokines generated in response to Flumist would (a) likely travel to the CNS, or (b) from outside

[28] To be clear, although Dr. Huq has consistently preferred a diagnosis of PRES, his first report cited literature which he contends supports a direct relationship between post-vaccination inflammation and stroke. (Ex. 24, pp. 7-8.) However, after respondent's experts disputed that contention (Ex. A, pp. 6-7), Dr. Huq's second report reiterated that "it is more likely AJK had PRES rather than stroke" and further added that "[i]f we call it stroke, the stroke probably occurred via PRES." (Ex. 133, p. 1.) Subsequently, petitioners' prehearing brief explained that, although there is no dispute that A.J.K. suffered an occipital stroke two days after vaccination, "[p]etitioners' theory of causation, which is explained and supported by an expert neurologist and an expert immunologist, is that A.J.K.'s vaccinations caused an innate immune reaction involving a release of proinflammatory cytokines that acted synergistically with A.J.K.'s resolving virus (HFMD) leading to a disruption of the blood brain barrier, endothelial injury and, ultimately, PRES." (ECF No. 126, p. 14.)

the blood-brain barrier stimulate a response within, or (c) upregulate in sufficient amounts (and type) to impact a child with a hippocampal abnormality and thereby further lower his seizure threshold" (footnote omitted)). Even where there is some reason to suspect a condition may be cytokine mediated, this does not automatically lead to the conclusion that vaccines can cause the injury merely because vaccines produce some cytokine elevations. *See, e.g.*, *Dean ex rel. I.D. v. Sec'y of Health & Human Servs.,* No. 13-808V, 2017 WL 2926605, at *17-18 (Fed. Cl. Spec. Mstr. June 9, 2017) (explaining in the context of alleged encephalopathy that, even though "[m]any of the general principles (as evidence by Petitioner's expert reports plus the filled medical or scientific literature) that underlies this theory are not disputed," "[t]he most immediately apparent weakness in this case's causation theory is the heavy lifting it assigns to the post-vaccination cytokine production process as the cause of almost all of the pathologic effects of the vaccines at issue"); *Bohn ex rel. G.B. v. Sec'y of Health & Human Servs.*, No. 16-0265V, 2021 WL 4302367, at *16-21 (Fed. Cl. Spec. Mstr. Aug. 23, 2021) (explaining that petitioner's experts sought "to marry via *ipse dixit* literature showing elevated proinflammatory post-vaccination cytokines on the one hand with literature showing SCLS and cytokine storm as being injurious cytokine-mediated conditions on the other," but that "the literature filed in this case demonstrates only that cytokine levels observed post-vaccination are dramatically lower than the levels of cytokines measured in those experiencing injurious systemic cytokine reactions"); *Chavez ex rel. T.C. v. Sec'y of Health & Human Servs*., No. 16-1479V, 2022 WL 3368502, at *24 (Fed. Cl. Spec. Mstr. July 19, 2022) (explaining that "[m]edical literature filed by petitioner supports the proposition that proinflammatory cytokines may play a role in the development of fever, which may lead to seizures and epilepsy" but that "[t]he literature does not support the notion that afebrile seizures are triggered by vaccination").

i. Petitioners have presented preponderant evidence that PRES can be cytokine-mediated

PRES is a clinical-radiological syndrome characterized by a variable combination of headaches, seizures, altered mental status, visual impairment, focal neurological signs and symmetric vasogenic edema in bilateral posterior cerebral circulation territory. (*See* Chen et al., *supra* Ex. 47, p. 93.) However, the symptoms and signs of PRES are not specific and can be seen in many other neurological disorders. (Fugate & Robinson, *supra* Ex. 68, p. 918.) As the experts in this case explained (*See, e.g.*, Tr. 70), PRES is a relatively new diagnostic entity, though it is one that is increasingly recognized in clinical practice. (*See* Chen et al., *supra* Ex 47, p. 93; Hobson et al., *supra* Ex. 84, p. 590.) However, PRES remains poorly understood. (Hobson et al., *supra* Ex. 84, p. 590.) There is no definitive explanation for how PRES happens.

As Dr. Huq and Dr. Forsthuber have both described, there are two leading theories regarding the pathophysiology of PRES: 1) the "hyperperfusion theory," where a rapid increase in arterial blood pressure leads to cerebral hyperperfusion, vascular leakage, and vasogenic edema; and 2) the "toxic" theory, where endothelial dysfunction is caused by circulating endogenous or exogenous "toxins." (Fischer & Schmutzhard,

supra Ex. 66, p. 1609 (also filed as Ex. A, Tab 7).) A variation of the "toxic" theory proposes that endothelial cell dysfunction of arterial blood vessels in the brain is triggered by excessive release of proinflammatory cytokines or other inflammatory mediators, resulting in endothelial activation, release of vasoactive mediators, increased vascular permeability, and edema formation. (*Id.*) "This mechanism is regarded as the key feature causing PRES in patients with autoimmune disorders or sepsis." (*Id.* at 1609-10.) Petitioners in this case rely on the "toxic theory," contending that A.J.K.'s vaccinations resulted in a release of proinflammatory cytokines and inflammation that acted synergistically with A.J.K.'s resolving viral infection (HFMD) leading to a disruption of the blood-brain barrier, endothelial injury and, ultimately, PRES. (ECF No. 126, p. 17; Tr. 123-24, 237.) The likely mechanism involves proinflammatory cytokines generated by the vaccinations altering the blood-brain barrier and either facilitating the entry of virus into the brain or directly causing cytokine-mediated endothelial injury.[29] (ECF No. 126, p. 17 (citing Ex. 165 (Dr. Gershwin's first supplemental report)).)

This theory is supported in the broadest sense by the observation that PRES is usually associated with a systemic inflammatory process, such as sepsis, eclampsia, transplantation, and autoimmune disease. (Bartynski, *supra* Ex. 37, p.1046-47.) Chen et al. postulated a theory of immune system activation in the pathogenesis of PRES. (Zheng Chen et al., *Immune System Activation in the Pathogenesis of Posterior Reversible Encephalopathy Syndrome,* 131 BRAIN RSCH. BULL. 93, 94 (2017) (Ex. 47).). During inflammation, Dr. Huq theorizes that IL-1 "induces expression of ICAM-1 and VCAM-1 on endothelium which in turn facilitates the interaction of leukocytes with endothelium leading to endothelial damage." (Ex. 24, p. 10; *see also* Chen et al., *supra* Ex. 47, p. 96.) Immune system activation in PRES also causes the release of cytokines, such as TNF-α, that upregulate the expression of vascular endothelial growth factor ("VEGF"), which plays an important role in increasing vascular permeability. (Ex. 24, p. 10; *see also* Bartynski et al., *supra* Ex. 37, p. 1047; Chen et al., *supra* Ex. 47, p. 96-97.) Additionally, many PRES-related conditions induce T cell activation, cytokine release, and subsequent leukocyte adhesion and activation, resulting in endothelial damage and fluid leakage. (Chen et al., *supra* Ex. 47, p. 93.) Thus, even as uncertainty remains, the medical literature on PRES supports the thinking that immune system activation and endothelial dysfunction can play a critical role in the pathogenesis of PRES. (*See id.* at 96-98.)

On respondent's behalf, Dr. Bingham agrees from a neurology perspective that there is a "reasonable" model for PRES involving endothelial dysfunction, though he suggests an immune theory remains to be proven. (Tr. 299-300.) Dr. Bingham agreed that hypertension only accounts for about 80% of PRES cases, but he disclaimed any ability to determine whether cytokines are involved in the pathogenesis of the remaining cases, explaining that "we don't measure cytokines in clinical cases, so it's hard to

[29] The suggestion that PRES may have resulted from entry of the virus into the brain has not been the focus of this case. Although Dr. Huq posited this in the alternative, he explained that he is not aware of any literature showing PRES to be a neurologic complication of HFMD and, when it is associated with infection, PRES usually results from bacterial infection. (Tr. 122, 124.) Dr. Gershwin agreed that direct entry of the virus into the brain is possible but indicated that direct entry of the virus into the brain is not necessary to his opinion. (Tr. 258.)

make an opinion about . . . what their role may be, especially in cases where there is no hypertension." (Tr. 301.) From an immunology perspective, however, respondent's other expert, Dr. Forsthuber, agrees that cytokines affecting the blood-brain barrier is "for sure a valid concept." (Tr. 354.) Moreover, he agrees that sepsis (discussed above as one of the conditions associated with PRES) can produce sufficient cytokines to disrupt the blood-brain barrier. (Tr. 387-90.) Further, Dr. Forsthuber agrees that a number of the conditions associated with PRES are characterized by systemic immune activation or dysregulation, though he stresses that immune mechanisms more likely account for a minority of cases (about 20%). (Tr. 378-79.)

In light of all of the above, and considering the record as a whole, there is preponderant evidence that PRES, though somewhat novel and not fully understood, is a recognized condition and that current thinking includes disruption of the blood-brain barrier via cytokine activity as among the viable theories thought to potentially explain at least a subset of PRES cases. However, this is not the entirety of what petitioner must show under *Althen* prong one. The key remaining question is whether petitioner can show that the cytokine response to vaccination is capable of causing or contributing to this process.

ii. Petitioners have not presented preponderant evidence that vaccines, even in combination with infection, can cause PRES.

Although some PRES cases may be theorized as cytokine-mediated as petitioners urge, none of the above-discussed literature regarding PRES posits vaccination as a cause or trigger of PRES. Thus, respondent's experts urge that vaccines are not generally accepted as causes of PRES. (Tr. 292 (Dr. Bingham); Tr. 325 (Dr. Forsthuber).) During the hearing, petitioners' experts likewise confirmed that there is no literature directly on point. (Tr. 140 (Dr. Huq); Tr. 253-54 (Dr. Gershwin).)

The two available case reports provide some evidence supporting petitioner's theory, but they are insufficient without more. (*See* Aydin et al., *supra* Ex. A, Tab 8 (also filed as Ex. 34); Hamano et al., *supra* Ex. A, Tab 9 (also filed as Ex. 74).) Case reports are, in general, weak evidence given that they are, by nature, anecdotal.[30] Moreover, any reliance on these specific case reports is undercut by Dr. Gershwin's testimony specifically disclaiming that A.J.K.'s vaccines alone could have caused her condition, which is the scenario posited by the case report authors. (Tr. 235 (Dr.

[30] Petitioners in this program often highlight the usefulness of case reports in cases of rare diseases or unusual occurrences. *See, e.g.*, *Patton v. Sec'y of Health & Human Servs.*, 157 Fed. Cl. 159, 166-67 (2021). However, case reports "'do not purport to establish causation definitively, and this deficiency does indeed reduce their evidentiary value,'" even though they are not entirely devoid of evidentiary value. *Paluck ex rel. Paluck v. Sec'y of Health & Human Servs.*, 104 Fed. Cl. 457, 475 (2012) (quoting *Campbell v. Sec'y of Health & Human Servs.*, 97 Fed. Cl. 650, 668 (2011), *aff'd*, 786 F.3d 1373 (Fed. Cir. 2015)); *see also Crutchfield v. Sec'y of Health & Human Servs.*, No. 09-0039V, 2014 WL 1665227, at *19 (Fed. Cl. Spec. Mstr. Apr. 7, 2014) ("[S]ingle case reports of Disease X occurring after Factor Y . . . do not offer strong evidence that the *temporal* relationship is a *causal* one—the temporal relationship could be pure random chance."), *aff'd*, 125 Fed. Cl. 251 (2014).

Gershwin stating, "I don't think the vaccinations alone would have done it.").) Instead, petitioners' experts opine that A.J.K.'s ongoing adaptive immune response, due to her resolving HFMD and secondary infections, coupled with the additional effects of her multiple vaccinations, combined to synergistically cause sufficient endothelial disruption of the blood-brain barrier to ultimately cause PRES.

Given the novelty of this assertion, Dr. Gershwin's explanation of the underlying immunology is critical to petitioner's *Althen* prong one showing. "Of course, petitioners are never required to establish [a] mechanism—but they often attempt to do so, and therefore it is reasonable to evaluate their success in in their effort." *Howard v. Sec'y of Health & Human Servs*., No. 16-1592V, 2022 WL 4869354, at *24 (Fed Cl. Spec. Mstr. Aug. 31, 2022), *review denied sub nom. Howard v. United States*, No. 16-1592V, 2023 WL 4117370 (Fed. Cl. May 18, 2023), *appeal filed sub nom. Howard v. HHS*, No. 23-1816 (Fed. Cir. Apr. 28, 2023). The Court of Federal Claims has previously explained that while the *Althen* Court rejected the need for scientific certainty, "in 'a field bereft of complete and direct proof of how vaccines affect the human body,' . . . [t]he standard of proof does not operate as a sliding scale that varies depending upon the quantity and quality of the scientific evidence that is available." *Caves v. Sec'y of Health & Human Servs*., 100 Fed. Cl. 119, 143 (2011) (quoting *Althen*, 418 F.3d at 1280), *aff'd*, 463 F. App'x 932 (Fed. Cir. 2012).

In advancing his theory, Dr. Gershwin disclaims any need or ability to distinguish between different cytokines as a practical reality and further suggests that his theory does not require a "burst" or "slug" of post-vaccination cytokines. (Tr. 211, 214, 222-23.) During the hearing, Dr. Gershwin cited a paper by Herve et al. for the proposition that cytokines can have systemic effect without creating constitutional symptoms, such as fever or malaise. (Tr. 216-17 (citing Herve et al., *supra* Ex. 182, p. 39).) Further to that, he cited experimental studies, such as those by Skibinksi et al., Nichols et al, Melgaco et al, De Rosa et al., and Wang et al., as evidence that vaccinations increase circulating cytokines. (Tr. 219-20; Ex. 147, p. 2 (citing P.J. Dias & S. Gopal, *Refractory Thrombotic Thrombocytopenic Purpura Following Influenza Vaccination*, 64 ANAESTHESIA 444, 445 (2019) (Ex. 137); Nichols et al., *supra* Ex. 148; Melgaço et al., *supra* Ex. 149; De Rosa et al., *supra* Ex. 150; Skibinksi et al., *supra* Ex. 183). Further still, Dr. Gershwin cited studies by Bonney et al. and de Vries et al. to demonstrate that cytokines can, in combination with viral infection, increase the permeability of the blood-brain barrier.[31] (Tr. 251-52; de Vries et al., *supra* Ex. 168; Stephanie Bonney et al., *Gamma Interferon Alters Junctional Integrity via Rho Kinase Resulting in Blood-Brain Barrier Leakage in Experimental Viral Encephalitis*, MBIO, July/August 2019 (Ex. 176); *see also* Ex. 165.) The de Vries and Bonney studies implicate specific cytokines (TNF-α, IL-1β, INF-γ, and IL-6) as potential mediators of the endothelial junctions that determine the permeability of the blood-brain barrier. (de Vries et al., *supra* Ex. 168; Bonney et al., *supra* Ex. 176.)

[31] Alternatively, Dr. Huq also suggested that the vaccines could have contributed to viral mutagenesis. However, he agreed that he was not presenting that possibility to a more likely than not standard and acknowledged, "I think I don't have any evidence to show for that." (Tr. 123.)

On respondent's behalf, Dr. Forsthuber persuasively challenges all of this. As noted above, Dr. Forsthuber does not dispute that cytokines affect the blood-brain barrier. (Tr. 354-58.) Nor does he dispute that vaccinations produce some cytokines. (*Id.* at 336-37.) However, he stresses a mismatch between the magnitude of the cytokine response that can be expected following vaccination and the magnitude of cytokine activity necessary to disrupt the blood-brain barrier.

Importantly, notwithstanding the overall contours of his opinion, Dr. Gershwin did likewise effectively acknowledge that the question of magnitude matters. Asked if there would be correlation between the degree of blood-brain barrier opening and the degree of edema, he responded, "Absolutely." (*Id.* at 267.) He explained that "this had to be a significant disruption of the endothelial cells, because I don't think a minor disruption would make any difference." (*Id.*) When he was asked, in turn, whether there is a correlation between the magnitude of a cytokine response and the degree of endothelial dysfunction, he responded that "it's either related to the magnitude or the balance." (*Id.* at 267-68.) By "balance," Dr. Gershwin explained that the question of magnitude may relate to the "relative," rather than "absolute," levels among different cytokines. (*Id*. at 268.) However, even as Dr. Gershwin sought to avoid the specific question of quantifying cytokines, he relied throughout his testimony on more indirect assertions that some form of meaningfully robust cytokine response is present. For example, he testified during rebuttal: "So on the other point [Dr. Forsthuber] made regarding that issue of doses, you know, his view of vaccination is much more benign than mine. I don't mean to imply that my impression of vaccination is malignant. It certainly isn't. But it is an active, aggressive process." (*Id.* at 401.) In that regard, examination of the de Vries and Bonney papers cited by Dr. Gershwin confirms that he actually relies on studies that identify specific cytokines (TNF-α, IL-1β, INF-γ, and IL-6) at specific levels (in the nanogram per milliliter range) as affecting the blood-brain barrier. On this record, he has only established these particular parameters. Without the framework support from these papers, Dr. Gershwin's suggestion that *any* imbalance in cytokines could support his theory would tip into pure speculation.[32] In fact, when Dr. Gershwin was

[32] While Dr. Gershwin may be correct to caution that understanding of cytokines in any real world context is nuanced and incomplete, there were indications during the hearing that Dr. Gershwin took this caveat too far. For example, Dr. Gershwin was asked on direct examination, "For purposes of understanding your theory of causation, how concerned do we have to be about the different kinds of cytokines that can be produced following vaccination?" He responded, "You can't. You can't for lots of reasons, one of which is that . . . . we can't be too concerned in terms of saying, which cytokine was it or which vaccine was it. It's a bit like the Casablanca at the end where it says, Round up all the usual suspects." (Tr. 222-23.) However, it is very difficult to square this with the evidence of record that includes specific studies cited by Dr. Gershwin demonstrating experimentally that specific cytokines can affect the blood-brain barrier. Nor is it the case that science is completely in the dark regarding the functions of different cytokines. (*See , e.g.*, Atmaram Yarlagadda et al., *The Blood Brain Barrier and the Role of Cytokines in Neuropsychiatry*, 6 PSYCHIATRY (EDGEMONT) 18, 18 (2009) (Ex. 169) (categorizing cytokines as either pro-inflammatory, anti-inflammatory, or hematopoetic).) Regarding a different point, Dr. Gershwin asserted in a discussion of changes in the field of immunology that "people don't use textbooks anymore, by the way." (Tr. 254.) However, Dr. Forsthuber pushed back strongly on that comment, stating "maybe at University of Texas we're teaching differently, but excuse me. We are using textbooks still to teach our students immunology. And, yes, the field moves rapidly, and I know of this, but the basics are taught [and] the textbooks are used to teach our students immunology. And even I go back to textbooks, and I look up fundamental things . . . ." (Tr. 358.) Dr. Forsthuber's point is well taken, in that while Dr.

prompted on cross-examination to identify what level of cytokines are necessary to affect the blood-brain barrier, he did specifically cite the study by de Vries et al. (*Id.* at 251-52.)

The de Vries et al. study explained that TNF-α, IL-1β, and IL-6 are three cytokines that have been implicated in the pathology of central nervous system diseases. (*See* de Vries et al., *supra* Ex. 168, p. 38.) The authors set out to examine in vitro whether these specific cytokines could induce changes in the integrity of the blood-brain barrier. (*Id.* at 38-39.) The study used "trans endothelial electrical resistance" ("TEER") as a proxy for the integrity of the endothelial tissue, meaning that a decrease in TEER signified an increase in blood-brain barrier permeability. (*See id.*) In their discussion, the study authors suggested significance in their finding that 50 ng/mL—that is 50 *nanograms* per milliliter—of TNF-α and 100 ng/mL of IL-1β produced a temporary (210 minute) 50% decrease in TEER. (*Id*. at 41.) IL-6 produced a more gradual, but non-reversible decline in TEER. (*Id*. at 42.) The effects of administering these cytokines within the model was dose dependent with, for example, administrations at 50 ng/mL producing a stronger effect than 1 ng/mL for both TNF-α and IL-1β. (*Id*. at 39-40.) For IL-6 in particular, Dr. Forsthuber stressed that the study showed that, while a 100 ng/mL dose had a gradual effect, a 1 ng/mL dose produced no response. (Tr. 356-58; de Vries et al., *supra* Ex. 168, p. 40.)

Thus, Dr. Forsthuber explains that de Vries et al. show that it likely takes a dose of nanograms per milliliter, or more specifically at least 10 ng/mL of IL-6, to affect the permeability of the blood-brain barrier at all. (Tr. 357.) However, discussing how the de Vries study demonstrated the cytokine levels necessary to affect the blood-brain barrier, Dr. Gershwin testified that the in vitro study used cytokines "in the picogram to nanogram range," which "is well within the parameters of what you would expect to happen in somebody who is having a change in their blood-brain barrier as seen here." (*Id.* at 251-52.) But, as Dr. Forsthuber explained, "[A] picogram is actually one trillionth of a gram. So, . . . a thousand picograms would be one nanogram, and a thousand nanograms would be one microgram." (*Id.* at 339.) Thus, a nanogram is three orders of magnitude larger than a picogram. To suggest that anything in the "picogram to nanogram range" would be germane is to effectively sidestep the question.[33]

The reason this is significant is because the studies of record measuring post-vaccination cytokine production tend to show much lower quantities, measured in

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Gershwin may certainly propose a theory on the cutting edge of immunology, his theory, if it is to be considered sound and reliable, must be grounded in *something* that has been established in the field.

[33] As previously explained, Dr. Gershwin alternatively suggested that it is equally plausible that an imbalance in cytokines could be causal, rather than the absolute magnitude of cytokines. (Tr. 268.) He stressed that "cytokines and their effect may be modulated by each other . . . . [i]t may be a relative balance amongst all of them . . . ." (*Id.*) On this record, however, that still sidesteps the key question. Imbalances still have magnitudes, and on this record, the dose at which cytokines can be viewed as causal has been evidenced experimentally by the de Vries et al. and Bonney et al. studies but would otherwise remain unproven.

picograms per milliliter, rather than nanograms per milliliter.[34] Respondent also filed a study by Kashiwagi et al. that examined the effects of the administration of multiple vaccines. (*See* Kashiwagi et al., *supra* Ex. A, Tab 16.) The in vitro portion of the study stimulated samples with different combinations of vaccines. Mean values of IL-β, IL-6, and TNF-α levels—the same three cytokines examined by de Vries et al.—were generally higher with concurrent stimulation with multiple vaccines, but not uniformly so and without any correlation between the number of vaccines and higher cytokine levels. (*See id.* at 682, tbl.2.) Therefore, while administration of multiple vaccinations may produce some added increase in cytokine levels compared to a single vaccine, there is evidence refuting any assumption that there is any simple additive or multiplying effect. (Tr. 351-53.) Even with administration of multiple vaccines, Kashiwagi et al. showed cytokine levels remaining below the levels at which blood-brain barrier disruption could be theorized.[35]

Dr. Forsthuber persuasively suggests that de Vries et al. confirm that the relatively slight increases in cytokines experienced post-vaccination, generally in the picogram range, are unlikely to change the blood-brain barrier, which the evidence on this record suggests occurs at cytokine levels in the nanogram range. (Tr. 357-58.) Indeed, the importance of the distinction between studies involving picograms versus nanograms of cytokines has also been observed in prior cases. *See, e.g.*, *Brunson ex*

[34] For example, Skibinski et al. found within human samples that post-flu vaccination IFN-γ peaked at 257.89 *picograms* per milliliter ("pg/mL") for an adjuvanted formula, TNF-α peaked at 212.66 *pg*/mL, and IL-6 peaked at 15,465.00 *pg*/mL. (Skibinski, *supra* Ex. 183, p. 6, tbl.1.) Melgaço et al. found that an acute hepatitis A infection resulted in cytokine production (IL-6, IL-10, TNF, and IFN-γ) ranging from 31.2 to 159.1 pg/mL whereas a first dose of hepatitis A vaccine produced cytokines ranging from 55.73 to 237.89 pg/mL, expect for IL-6 which was 10,043.1 pg/mL. (Melgaço, *supra* Ex. 149, p. 4, tbl.1.) Dhiman et al. found that vaccination against Rubella produced median IL-6 of 3,681.0 pg/mL (interquartile range of 3,160.0 to 4,052.0), TNF-α of 29.7 pg/mL (interquartile range of -7.0 to 89.2), and IFN-γ of 8.5 pg/mL (interquartile range of 3.0 to 23.4). (Neelam Dhiman et al., *Predominant Inflammatory Cytokine Secretion Pattern in Response of Two Doses of Live Rubella Vaccine in Healthy Vaccinees*, 50 CYTOKINE (2010) (manuscript at 12, tbl.2) (Ex. 54).) Eriksson et al. observed statistically significant increases in INF-γ, IL-6, TNF-α, and IL-1β, one week post- flu vaccination; however, none of those elevations reached 1,000 pg/mL, *i.e.*, a nanogram. (Jens-Christian Eriksson et al., *Local and Systemic Cytokine and Chemokine Responses After Parental Influenza Vaccination*, 1 INFLUENZA & OTHER RESPIRATORY VIRUSES 139, 143, fig.3 (2007) (Ex. 154).) It should also be noted that both parties' immunology experts stress the limitations of these measurements. Measuring cytokines in vivo is not necessarily realistic. Most studies use a process by which blood or serum samples are drawn from subjects to create cultures of immune cells that are then stimulated to produce cytokines in vitro. (Tr. 341-42, 346.) Dr. Forsthuber seems to imply that these in vitro results may very well exaggerate what occurs in the body. (Tr. 336, 343-44.) Dr. Gershwin, by contrast, implies the in vitro results fail to capture all that may occur in the body. For example, he asserts that dendritic cells amplify the immune response post-vaccination. (Tr. 220-21 (citing Penelope A. Morel & Michael S. Turner, *Designing the Optimal Vaccine: The Importance of Cytokines and Dendritic Cells*, 3 OPEN VACCINE J. 7 (2010) (Ex. 184)).)

[35] IL-1β levels remained below one nanogram per milliliter in all combinations. TNF-α exceeded one nanogram per milliliter (reaching 1,833 pg/mL and 1,484 pg/mL) with only certain combinations of vaccine. (Kashiwagi et al., *supra* Ex. A, Tab 16, p. 679.) As with the other studies, IL-6 was generally higher than TNF-α and IL-1β, ranging from 1,872 to 4,137 pg/mL. (*See id.*) In all instances, the observed mean value did not exceed 5,000 pg/mL for any cytokine under any combination of vaccinations. (*See id.* at 678, fig.1.)

rel. T.A. v. Sec'y of Health & Human Servs., No. 17-530V, 2020 WL 5755502, at *13 n.12 (Fed. Cl. Spec. Mstr. Sept. 3, 2020); *Nunez v. Sec'y of Health & Human Servs.*, No. 14-863V, 2019 WL 2462667, at *31 (Fed. Cl. Spec. Mstr. Mar. 29, 2019), *review denied*, 144 Fed. Cl. 540 (2019), *aff'd*, 825 F. App'x 816 (Fed. Cir. 2020); *Copenhaver v. Sec'y of Health & Human Servs.*, No. 13-1002V, 2016 WL 3456436, at *13 n.22 (Fed. Cl. Spec. Mstr. May 31, 2016).

The collection of studies discussed above do include some mixed results wherein there are some instances of vaccination producing IL-6 up to the borderline of the magnitude that de Vries et al. found could begin to affect the blood-brain barrier. (*See supra* notes 34-35.) However, not all of the above studies included such findings. Moreover, as noted above, Dr. Gershwin agreed that his theory requires "a significant disruption of the endothelial cells, because I don't think a minor disruption would make any difference." (Tr. 267.) In any event, Dr. Gershwin does not rely on IL-6 in particular.[36] Instead, he indicated that specific cytokines could not be isolated as causally significant. (Tr. 222-23.) In that regard, Dr. Huq's discussion of PRES, discussed above, primarily implicates IL-1 and TNF-α, rather than IL-6, as meaningful to the toxic theory of PRES. However, none of the studies demonstrated either TNF-α or IL-1β reaching the nanogram scale examined by de Vries et al.

The remaining question is whether the cytokine response to vaccination, when combined with the response to infection, rises to a magnitude that could be expected to disrupt the blood-brain barrier. On that point, respondent has filed evidence indicating that a common HFM infection does not produce an outsized cytokine response, and instead produces cytokine responses in the picogram range.[37] These results are not necessarily surprising given that Kashiwagi et al. also demonstrated that an outpatient viral infection produces cytokines comparable to a vaccination. (Kashiwagi et al., *supra* Ex. A, Tab 16, p. 7 (explaining that "[c]ompared with acute phase of an influenza infection, cytokine profiles after vaccination were similar to those in mild-moderate outpatients infected with the 2009 pandemic strain").) In that regard, Dr. Forsthuber distinguishes common viral infections, such as HFMD, from much more serious

[36] By way of example, Dr. Forsthuber filed a study confirming that IL-6 strongly correlates to fever (*See* Engel et al., *supra* Ex. A, Tab 10, p. 10), but Dr. Gershwin indicates fever would not necessarily be present under his theory (Tr. 216-17).

[37] Specifically, respondent filed a study by Cai et al., which examined children admitted for hospitalization for HFMD. (*See* Cai et al., *supra* Ex. J, p. 2.) Among their findings, cases of mild HFMD had cytokine levels, including TNF-α, IL-1β, and IL-6, comparable to controls, mild HFMD produced 3.30 pg/mL of IL-1β, 4.20 of IL-6, and 4.7 pg/mL of TNF-α. (*Id*. at 4, tbl. 2.) Those with severe HFMD, defined as cases involving neurologic or cardiopulmonary complications, had higher cytokine levels. Among those cases, IL-1β was measured between 15.3 and 16 pg/mL, IL-6 was measured between 12.65 and 16 pg/mL, and TNF-α was measured between 19.85 and 25.4 pg/mL. (*Id*.) Another study, by Yu et al., of adults with HFMD found that those with the infection had approximately 10-times the IL-6 and about 14-times the TNF-α as compared to controls. (Linghua Yu et al., *Inflammatory Profiles Revealed the Dysregulation of Cytokines in Adult Patients of HFMD*, 79 INT'L J. INFECTIOUS DISEASES 12, 16 & tbl. 3 (2019) (Ex. G, Tab 8).) IL-1β was about the same, only slightly elevated. (*Id*.) However, the infected subjects still only had IL-6 levels of 174.15 pg/mL, TNF-α levels of 691.31 pg/mL, and IL-1β levels of 20.22 pg/mL. (*Id*.)

conditions, such as sepsis or gram negative bacterial infection, that have otherwise been known to disrupt the blood-brain barrier. (Tr. 387-90, 392-93.) Petitioner's own expert, Dr. Huq, stressed essentially the same point when testifying that it would be unlikely that HFMD would directly result in PRES. (Tr. 122.)

Dr. Gershwin suggests a synergism, and not merely an additive effect. This relies in substantial part on the Bonney paper, which Dr. Gershwin contends is evidence that IFN-γ makes viral infection more potent. (Tr. 251-52.) The authors explain that experiments show IFN-γ, though generally important as an antiviral signal, has the effect of contributing to blood-brain barrier leakage. (Bonney et al., *supra* Ex. 176, p. 1.) They further showed that blocking IFN-γ during an infection improved blood-brain barrier integrity.[38] (*Id*.) Dr. Forsthuber, however, stresses that, like the de Vries study, the Bonney study utilized 100 ng/mL of IFN-γ. (Tr. 362.) This is about 500 to 1,000 times the level of IFN-γ in a healthy individual and 50 to 100 times what is expected from a stimulated culture. (*Id.* at 362-63 (citing Kleiner et al., *supra* Ex. E, Tab 17).) Thus, Dr. Forsthuber explains that the study applies "super physiologic doses," rendering it purely theoretical with no practical application to what does, or does not, cause PRES. (*Id.* at 363.)

Without doubting that simultaneous infection and vaccination both contribute to an overall immune response, the Bonney study is inadequate to support Dr. Gershwin's and Dr. Huq's specific premise that vaccines and infections operate s*ynergistically* to create some greater effect on the blood-brain barrier.[39] The study simply provides some additional experimental evidence showing that cytokines—IFN-γ in particular—may affect the blood-brain barrier and, further, that it may help to explain how viral infections can sometimes result in encephalitis. It is not readily apparent that it would evidence either increased potency of the infection itself or that vaccines contribute to any greater synergistic immune response.

Finally, it is important to note that Dr. Gershwin asserts that experimental studies, such as Bonney and de Vries, do have clinical efficacy regardless of dose. (Tr. 400-01.) Yet, he also made a point of stressing that his theory is not proposing "a pharmacologic burst with super-normal levels of cytokines being produced." (*Id.* at 211.) This produces an inherent tension within Dr. Gershwin's opinion. Even accepting that a given study might provide some proof of a concept without reflecting a realistic dose response, it is still difficult to accept that Dr. Gershwin can affirmatively rely on studies examining the effects of "super physiologic" or "super-normal" levels of cytokines as the primary evidence his theory is even possible while simultaneously disclaiming the need for such cytokine levels in application. This is especially so given the lack of any other

[38] It should be noted the study authors discuss the results in the context of viral encephalitis, not PRES. (*See* Bonney et al., *supra* Ex. 176, pp. 14-16.)

[39] To be clear, the issue discussed herein is petitioners' inability to substantiate this theory. If proven, the concept of vaccination operating in connection with infection to cause injury can present a legally tenable theory under *Althen* prong one. *See Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352 (Fed. Cir. 1999) (concluding that, under the Act, "an action is the 'legal cause' of harm if the action is a 'substantial factor' in bringing about the harm").

robust evidence suggesting vaccines can cause or contribute to PRES. Nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder ex rel. Snyder v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 743 (2009) (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997)); *see also Isaac v. Sec'y of Health & Human Servs*., No. 08-601V, 2012 WL 3609993, at *17 (Fed. Cl. Spec. Mstr. July 30, 2012) ("The weight to be given to an expert's opinion is based in part on the size of the gap between the science and the opinion proffered."), *aff'd*, 108 Fed. Cl. 743, *aff'd*, 540 F. App'x 999 (Fed. Cir. 2013).

For all the reasons discussion above, I find that petitioners have not satisfied their burden under *Althen* prong one. Although petitioners are persuasive in asserting both that cytokines can disrupt the blood-brain barrier, and that PRES specifically can be theorized in at least some instances to be a cytokine-mediated condition, only two case reports out of all the PRES literature filed in this case purport to associate any vaccine with PRES. This constitutes only minimal evidence of a potential causal relationship. In that context, Dr. Gershwin was not ultimately persuasive in setting forth a further explanation as to how synergism between a vaccine and infection could produce a sufficient cytokine response to open or disrupt the blood-brain barrier such that it could be implicated as a potential cause of PRES. Rather, the evidence of record suggests this is unlikely for the reasons discussed by Dr. Forsthuber.

a. *Althen* prong 3

The third *Althen* prong requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1278. That term has been equated to the phrase "medically-acceptable temporal relationship." *Id.* at 1281. A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." *de Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one's requirement). *See id.*; *Shapiro v. Sec'y of Health & Human Servs.*, 101 Fed. Cl. 532, 542 (2011), *reconsideration denied after remand*, 105 Fed. Cl. 353 (2012), *aff'd per curiam*, 503 F. App'x 952 (Fed. Cir. 2013); *Koehn v. Sec'y of Health & Human Servs.*, No. 11-355V, 2013 WL 3214877, at *26 (Fed. Cl. Spec. Mstr. May 30, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

A.J.K. received the vaccinations at issue during a wellness encounter that occurred around 10:00AM on September 29, 2014. (Ex. 3, p. 310; Ex. 1.) Given that A.J.K. was documented as previously experiencing twitching attributed to myoclonus, it would be difficult to place onset based on twitching alone. However, when A.J.K.'s mother first contacted the pediatrician at around noon on October 1, 2014, she reported that A.J.K. was "twitching and lethargic" since the night before and vomited that day. (Ex. 3, p. 309.) More specifically, she reported putting A.J.K. to bed at 7:30PM on the evening of September 30, 2014, and found her to be difficult to wake at 7:45AM the next

morning and inactive the entire morning. (*Id*.) Accordingly, the record reflects that symptoms consistent with PRES were first observed on the morning of October 1, 2014, just a few hours shy of 48 hours post-vaccination.

Dr. Gershwin opines that this is "perfect" timing for an innate immune response.[40] (Tr. 240-41.) Dr. Forsthuber likewise agreed on respondent's behalf that the innate immune response occurs within hours to days in general. (*Id.* at 381.) Although Dr. Forsthuber raised concerns regarding the time needed to generate an adaptive immune response, Dr. Gershwin explained that, while the HFM infection would have amplified the response insofar as it was still producing cytokines, the presence of the adaptive immune response to the HFMD is irrelevant vis-à-vis timing of onset. (*Id.* at 241-42.) Further to this, the literature filed in this case explains that PRES generally manifests over hours to days. (Hobson et al., *supra* Ex. 84 (PRES "presents with rapid onset of symptoms"); Liman et al., *supra* Ex. C, Tab 4 ("PRES is typically characterized by acute onset of neurological symptoms"); Fischer & Schmutzhard, *supra* Ex. A, Tab 7 ("onset may be acute or subacute, with symptoms developing within a few hours up to several days or even weeks").) Accordingly, without accepting that vaccines in particular can cause PRES, it is nonetheless reasonable to conclude that onset of PRES could occur within two days of an innate immune trigger.

Dr. Forsthuber expressed skepticism regarding the timing for an adverse event following vaccination, but this is less persuasive in light of the above. Specifically, he noted that adverse reactions to live vaccines, such as the MMR and varicella vaccines at issue, typically occur approximately 7 to 10 days post-vaccination. (Tr. 370.) Mild reactions to the flu vaccine, not including anything similar to what is at issue in this case, typically occur within 24 hours of vaccination. (*Id.* at 370-71.) Ultimately, he acknowledged that the appropriateness of the timing "cannot be 100 percent ruled out" but is "less appropriate." (*Id.* at 371.) He stressed that the two case reports included in this record that examined PRES following MMR vaccination had onsets between 4 and 10 days post-vaccination. (*Id.* at 370; Aydin et al., *supra* Ex. A, Tab 8, p. 525; Hamano et al., *supra* Ex. A, Tab 9, pp. 124-25.) Importantly, however, while the Hamano case report subject did have a worsening of symptoms at 4 days post-vaccination, the authors actually placed onset of her PRES at 8 hours post vaccination. (Hamano et al., *supra* Ex. A, Tab 9, p. 125.) They specifically note that this hours-long onset helped distinguish the case diagnostically from acute disseminated encephalomyelitis ("ADEM"), which they note typically occurs at least two days post-vaccination. (*Id.*)

b. *Althen* prong 2

The second *Althen* prong requires proof of a logical sequence of cause and effect, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375-77; *Capizzano*, 440 F.3d at 1326; *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). In establishing that a vaccine "did cause" injury, the opinions and views of the injured party's treating

[40] Dr. Huq likewise agreed the timing is appropriate for an inflammatory process, but he deferred to Dr. Gershwin with respect to the timing of a cytokine response. (Tr. 130-31.)

physicians are entitled to some weight. *Andreu*, 569 F.3d at 1375-77; *Capizzano*, 440 F.3d at 1326 (noting that "medical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether 'a logical sequence of cause and effect show[s] that the vaccination was the reason for the injury'" (alteration in original) (quoting *Althen*, 418 F.3d at 1280)). Medical records are generally viewed as particularly trustworthy evidence because they are usually created contemporaneously with treatment of the patient. *Cucuras v. Sec'y of Health & Human Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993).

However, medical records and/or statements of a treating physician's views do not *per se* bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. *See* § 300aa-13(b)(1) (providing that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court"); *Snyder v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 745 n.67 (2009) ("[T]there is nothing . . . that mandates that the testimony of a treating physician is sacrosanct—that it must be accepted in its entirety and cannot be rebutted."). As with expert testimony offered to establish a theory of causation, the opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases. The views of treating physicians should also be weighed against other, contrary evidence also present in the record—including conflicting opinions among such individuals. *Hibbard v. Sec'y of Health & Human Servs.*, 100 Fed. Cl. 742, 749 (2011) (concluding that it was not arbitrary or capricious for the special master to weigh competing treating physicians' conclusions against each other), *aff'd*, 698 F.3d 1355 (Fed. Cir. 2012); *Caves v. Sec'y of Health & Human Servs.*, 100 Fed. Cl. 119, 136-37 (2011), *aff'd*, 463 F. App'x 932 (Fed. Cir. 2012); *Veryzer v. Sec'y of Health & Human Servs.*, No. 06-522V, 2011 WL 1935813, at *17 (Fed. Cl. Spec. Mstr. Apr. 29, 2011), *review denied*, 100 Fed. Cl. 344, 356 (2011), *aff'd per curiam sub nom.* 475 F. App'x 765 (Fed. Cir. 2012).

i. Treating physician opinions are inconclusive

In this case, treating physician opinions alone cannot resolve *Althen* prong two. Both parties find support for their preferred diagnosis among at least some of the treating physicians. (*See, e.g.*, Ex. 7, p. 51 (initial radiologist's MRI report reflecting a differential diagnosis that included both ischemia and PRES); Ex. 7, p. 2 (first treating neurologist, Dr. Trasmonte, diagnosing ischemic stroke, likely idiopathic, as a "preponderant" working diagnosis); Ex. 3, p. 241 (second treating neurologist, Dr. Hsieh, concluding MRI is more consistent with PRES and evidence "does not favor" a stroke)). Additionally, there is genuine suspicion of vaccine causation among the treating physicians, but not any conclusion supporting vaccine causation. (Ex. 3, p. 264 (Dr. Poulin remarking on February 13, 2015 that "[a]ssociation vs causation unknown but potential post imm encephalopathy in [differential diagnosis]."); Ex. 3, p. 259 (NP Howard providing information regarding the Program); Ex. 3, p. 239 (genetics specialist noting on April 27, 2015 that "[e]ncephalopathy post MMR has been described and this may be related to a side effect of the vaccination"); Ex. 3, p. 136 (allergist noting on June 8, 2016, that A.J.K.'s history is "rightly concerning for an adverse vaccine reaction

but there is no course to prove or disprove immunizations were causative"). *But see* Ex. 3, p. 100 (Dr. Hussey indicating on February 27, 2017, "course suspicious for other etiology than vaccination"). On the whole, and especially given the uncertainty in diagnosis, explicit causal opinions by the treating physicians, either for or against vaccine causation, are not robust. Accordingly, the expert assessments of the clinical course are significant.

ii. There is not preponderant evidence hypertension caused A.J.K.'s acute neurologic event

Respondent places significant emphasis on the presence of hypertension as part of the explanation of medical events in this case. In his first report, Dr. Bingham opined that "it appears most likely that hypertension contributed significantly to, and may have been the primary underlying cause of, [A.J.K.'s] condition." (Ex. C, p. 10.) However, there is conflicting evidence with regard to whether A.J.K. was experiencing hypertension at the time of her acute neurologic event and the record is ultimately inconclusive. Dr. Bingham's assessment is based on the presence of systolic blood pressure readings indicative of significant blood pressure elevations of up to 141 mmHg. (Tr. 285.) He explained that a systolic pressure of about 101 represents the cut off for normal blood pressure in a 12-month-old. (*Id*.) Dr. Huq, by contrast, suggested that mean blood pressure readings were not concerning. (*Id.* at 90-91.)

Dr. Bingham agrees on respondent's behalf that hypertension was not initially documented on October 1, 2014. (Ex. C, p. 8.) Instead, he assumes her hypertension must have been volatile, implying the highest blood pressure may have initially gone undetected. (*Id.* at 10.) However, this assumption of volatility is not well supported by the records. During transport from Valdosta to Macon, A.J.K.'s vitals were measured continuously during an approximately 150-mile ambulance ride of over several hours. (Ex. 9, pp. 38, 41.) As a result, eight separate blood pressure measurements were taken between 1:06AM and 3:10AM on the morning of October 2, 2014. (*Id.* at 38-39.) The EMTs recorded that her vitals remained within normal limits during transport and the resulting blood pressure measurements were relatively stable, with systolic pressure ranging from 95 to 102 and mostly falling below what Dr. Bingham identifies as the cut-off for normal blood pressure. (*Id.*; Tr. 285.)

As Dr. Bingham noted during testimony, A.J.K. did later have a documented range of systolic blood pressure during her hospitalization in Macon that reached up to 141. (Tr. 285; Ex. 7, p. 6.) This did raise a concern regarding the possibility of hypertension. (Ex. 7, p. 18; Ex. 11, p. 40.) However, the notes also indicate this was doubted, cautioning that "[s]everal of the higher BPs were taken when child is fussing." (Ex. 7, p. 18.) Dr. Bingham agrees that a child's fussing can affect the blood pressure results and that accounting for that is "part of the art and science" of obtaining the reading. (Tr. 302.) Ultimately, the records document that prior to discharge cardiology concluded A.J.K. was not hypertensive. (Ex. 7, p. 6.) The records further confirm that no treatment was initiated for hypertension during A.J.K.'s hospitalization. (Ex. 12, p. 5.) Nor is there any indication from A.J.K.'s hospital records that any of her physicians

at that time concluded her presentation (whether stroke or PRES) was attributable to hypertension.[41] In fact, Dr. Trasmonte specifically indicated that the work up performed to determine the etiology of A.J.K.'s diagnosed stroke was normal and hypertension was not among A.J.K.'s discharge diagnoses. (Ex. 7, pp. 2, 7.) During the hearing, Dr. Bingham ultimately indicated that he was "puzzled" by the lack of treatment for hypertension. (Tr. 303.) Although he suggested he is not satisfied with the information contained in the medical records, he testified that "[i]f it actually appears in the chart that the cardiologist explicitly dismissed hypertension, then I can accept that." (*Id.*)

When A.J.K. later followed up with a cardiologist, her blood pressure was measured as significantly elevated on two occasions about one and two months following her hospitalization. (Ex. 12, pp. 1, 7.) Again, however, these records question the reliability of the readings due to fussing and movement. (*Id*.) Nonetheless, A.J.K. was started on treatment for hypertension at that time, given her history. (*Id*.) But in any event, these records do not establish hypertension as an initiating cause of A.J.K.'s condition. Instead, they offer the opinion that the hypertension may itself be a consequence of A.J.K.'s acute neurologic injury. (*Id.* at 2; *see also* Ex. 5, p. 13.) Moreover, Dr. Bingham agrees that this would be possible. (Tr. 301.)

In light of all of this, although there is evidence that A.J.K. had some documented elevations in blood pressure, there is not preponderant evidence that A.J.K.'s acute neurologic event was caused by hypertension.

iii. <u>There is not preponderant evidence HFMD resulted in stroke</u>

An additional observation underlying both of respondent's experts' opinions is the idea that infections are an important risk factor for pediatric stroke. (Tr. 294 (Dr. Bingham); Tr. 324-26 (Dr. Forsthuber).) Thus, they opine that A.J.K.'s HFM infection was a likely contributor to what they opine was a stroke. (Ex. C, p. 10; Tr. 288, 294, 324.) However, while infection may generally be a risk factor for pediatric stroke, it is less likely to explain A.J.K.'s own history.

To the extent one concludes that Dr. Huq has arrived at the correct diagnosis for A.J.K., he explains that the recognized neurologic complications of HFMD do not include PRES. Instead, when HFMD results in rare neurologic complications, it generally results in brainstem encephalitis, acute flaccid paralysis, aseptic meningitis, or Guillain-Barré syndrome. (Tr. 118-22.) Moreover, when HFMD leads to neurologic complications, Dr. Huq and Dr. Bingham both explained that this usually occurs within three to five days of symptom onset. (*Id.* at 121 (Dr. Huq), 307 (Dr. Bingham).) Thus, it is unlikely that HFMD led directly to PRES. Indeed, Dr. Forsthuber explicitly disclaimed

[41] In his first report, Dr. Bingham cites Exhibit 11, page 40, for the proposition that the hospital team considered hypertension as a cause of A.J.K.'s stroke. (Ex. C, p. 3.) However, the cited record is an October 6, 2014 telephone report from A.J.K.'s father to the primary care provider reporting that hypertension "is suspected." (Ex. 11, p. 40.) That report is consistent with the suspicion of hypertension recorded at Exhibit 7, page 18, but predated the October 7, 2014 record confirming that cardiology ultimately concluded hypertension was not present. (Ex. 7, p. 6.)

any opinion that HFMD would have led directly to neurologic injury in this case, stressing it was instead only a risk factor for stroke. (*Id.* at 324.)

However, accepting that infections generally can be a risk factor for pediatric stroke, Dr. Forsthuber acknowledges that the post-infection risk of stroke peaks within three days of infection. (*Id.* at 328 (discussing Armin J. Grau et al., *Common Infections and the Risk of Stroke*, 6 NATURE REVS.: NEUROLOGY 681 (2010) (Ex. A, Tab 3).) Dr. Forsthuber stressed that the risk remained statistically elevated at seven days, but none of the studies cited are adequate to evidence the increased risk as persisting for any longer. (*Id.*) In particular, the Fullerton study examined stroke cases occurring up to six months following a first encounter for a minor infection, but concluded that only the cluster of cases occurring one-week post-infection were statistically significant. (Fullerton et al., *supra* Ex. A, Tab 4, p. 1462.)

In this case, A.J.K.'s HFMD symptoms were first documented in a call to her pediatrician on September 17, 2014, about two weeks prior to her October 1, 2014 emergency department presentation. (Ex. 3, p. 322; Ex. 10, pp. 5, 8.) Thus, she was beyond the period of elevated risk by the time of her acute event. Although Dr. Bingham provided testimony regarding possible reasons infection might lead to stroke, he confirmed his opinion is based on the associational data. (Tr. 294, 309-10.)

Dr. Forsthuber also highlights the inflammatory response to infection, rather than any particular microbial agent, as leading to the elevated risk of stroke. (Ex. A, p. 6; Grau et al., *supra* Ex. A, Tab 3, p. 2 ("key points").) However, a key aspect of respondent's experts' opinions is that A.J.K.'s HFM infection was resolving by the time of her vaccinations and that there was no evidence of an inflammatory state around the time of her acute neurologic event to support any logical sequence of cause and effect per petitioners' theory. (Tr. 323-24, 369 (Dr. Forsthuber), 294 (Dr. Bingham).) Especially given that A.J.K.'s own acute neurologic event occurred outside the established period of elevated risk for a post-infection stroke, respondent's experts' confidence that a systemic inflammatory state is absent must also undercut their own theory if it undercuts petitioners' theory.

iv. PRES is a reasonable diagnosis

As noted above, both stroke and PRES were within A.J.K.'s initial radiologic differential diagnosis. (Ex. 7, p. 51.) Her first neurologist, Dr. Trasmonte, felt the MRI and clinical evidence preponderated in favor of stroke. (*Id.* at 2.) Her second neurologist, Dr. Hsieh, reevaluated both the MRI and the clinical records and concluded stroke was less likely than PRES. (Ex. 3, p. 241.) "PRES is not mainly radiological; the clinical context and the judgment of the clinician are crucial to making the correct diagnosis." (Fugate & Rabinstein, *supra* Ex. 68, p. 918.) In that regard, both parties' experts agree that either stroke or PRES could explain A.J.K.'s initial presentation. (Tr. 98 (Dr. Huq indicating PRES can present as a "stroke-like event"), 289-90 (Dr. Bingham agreeing that stroke and PRES are not mutually exclusive explanations).) Apart from the circumstances of hypertension and the preceding HFM infection addressed

separately above, Dr. Bingham raises two more direct challenges to a PRES diagnosis. He contends details of A.J.K.'s MRI, specifically, the appearance of signal change on ADC and diffusion weighted imaging, are distinct from what is classically seen in PRES. (*Id.* at 287.) He also stresses that, as the name suggests, PRES should only be diagnosed where the condition has demonstrated itself to be reversible. (Tr. 289-90.) Dr. Huq persuasively addressed both of these points.

First, Dr. Bingham in effect disputes that PRES is the best interpretation of A.J.K.'s MRI if the MRI includes evidence of restricted diffusion. "Classic" or "typical" MRI findings supportive of a PRES diagnosis are T2 or FLAIR hyperintensities indicative of vasogenic edema. (Liman et al., *supra* Ex. C, Tab 4, p. 29.) However, restricted diffusion would generally be indicative of cytotoxic edema, which would be less common in PRES. (*Id.* at 29-30.) In fact, larger areas of restricted diffusion may be indicative of ischemic stroke. (Fischer & Schmutzhard, *supra* Ex. C, Tab 5, p. 1612.) This point was raised by Dr. Trasmonte when he stated that:

> The other part of the differential of bioccipital hyperintensity on T2/FLAIR is PRES (posterior reversible encephalopathy syndrome). Typically however in PRES the diffusion weighted images would show either equivocal findings or if it is bright usually the ADC mapping images would not be dark as seen in this patient.

(Ex. 7, p. 2.) That is, although Dr. Trasmonte notes that A.J.K.'s T2/FLAIR imaging is consistent with PRES, restricted diffusion may be evidenced by additional signal change on either the diffusion weighted images or the ADC mapping images.[42]

Dr. Huq raises two important points responsive to this issue. First, the question of how much blackness is appropriate on the ADC mapping to confirm the genuineness of the restricted diffusion is a matter of clinical judgment, for which we have competing opinions from the treating neurologists given that Dr. Hsieh disagreed with Dr. Trasmonte's reading of the MRI on his re-review. (Tr. 85-86, 193-95.) After all, the imaging was sufficiently ambiguous that the radiologist initially included both stroke and PRES in the differential. (Ex. 7, p. 51.) Second, Dr. Huq opined that restricted diffusion, though it can be consistent with stroke, can also be consistent with PRES. (Tr. 84.) He cites literature that indicates that restricted diffusion can be seen in around 15 to 30 percent of PRES cases. (*Id.* at 102 (discussing Fugate & Rabinstein, *supra* Ex. 68, p. 919.).) Dr. Huq testified that, in his clinical experience, the MRI images in PRES can be "very variable," and that these "particular findings are totally consistent with PRES." (*Id.* at 85-86.) In fact, Dr. Huq has explained that the presence of some cytotoxic edema, *i.e.*, restricted diffusion on MRI, is consistent with the toxic theory of PRES. (*Id.* at 100-04.) Ultimately, Dr. Bingham conceded that A.J.K.'s initial MRI,

[42] Dr. Huq also explained that abnormalities on diffusion weighted images can sometimes be "shine through," or secondary signals due to the T2 FLAIR sequencing. (Tr. 193-94.) As Dr. Huq explains it, the blackness of the ADC mapping confirms that the abnormality on the diffusion weighted images is a true finding of restricted diffusion, rather than being "shine through." (Tr. 194.)

though it includes "a hint of an atypical pattern of signal change," is consistent with PRES. (*Id.* at 299.)

A.J.K. also had subsequent MRIs in January and May of 2015 that continued to show the bilateral occipital lobe lesions on T2/FLAIR. (Ex. 3, p. 58; Ex. C, p. 7.) According to Dr. Bingham, this is more consistent with stroke than PRES due to the fact that it demonstrates the encephalomalacic lesions to have been irreversible. (Ex. C, p. 7; Tr. 287-89.) In fact, Dr. Bingham testified that reversibility is a necessary part of the diagnostic criteria for PRES. (Tr. 291.) Although Dr. Bingham is correct that reversibility has been proposed as a diagnostic criterion (*see* Fischer & Schmutzhard, *supra* Ex. C, Tab 5, p. 1611-12 & fig. 3), no set of diagnostic criteria has been generally accepted (*Id*. at 1610.). Instead, the literature reflects that, while a majority of PRES cases will be reversible and will have a good prognosis, severe complications, including neurologic sequelae, may persist. (*Id*. at 1613.) Prior studies have confirmed pediatric cases of PRES resulting in long term epilepsy. (*Id*. at 1613-14.) Notably, whereas Dr. Trasmonte did not have the benefit of the subsequent MRIs, when Dr. Hsieh reevaluated A.J.K.'s initial MRI as more consistent with PRES than stroke, he had also reviewed A.J.K.'s later January 2015 MRI, which he remarked was notable for residual scarring. (Ex. 3, p. 241.) Thus, Dr. Bingham's opinion is not supported by the treating physicians. Dr. Huq further explained that the 15 to 30 percent of PRES cases that see restricted diffusion on MRI are also the PRES cases that are more likely to result in irreversible damage. (Tr.100-04; *see also* Liman et al., *supra* Ex. C, Tab 4, pp. 29-30.)

Additionally, Dr. Huq contends, consistent with Dr. Hsieh's opinion, that stroke is a less likely diagnosis. (Tr. 86.) Indeed, Dr. Trasmonte himself characterized the initial stroke diagnosis as a "working impression" that was "preponderate," rather than certain. (Ex. 7, p. 2.) Dr. Huq further stresses that the diffusion restriction potentially evidenced on the first MRI is the only evidence of ischemia. (Tr. 86.) But that finding is not necessarily exclusive to ischemia. (*Id*.) Moreover, the specific presentation of a biocciptial stroke would be very unusual in a child. (Tr. 84.) Furthermore, Dr. Bingham's diagnostic assessment overall, and therefore also his degree of concern regarding how classic or typical the MRI findings are for PRES, was informed at least in part by his reliance on both hypertension and the preceding HFM infection as contributors to stroke. However, as discussed above, I have found the evidence does not clearly support those assumptions. This greatly reduces the attractiveness of stroke as an alternative diagnosis. Moreover, apart from stressing the general reversibility of PRES, Dr. Bingham testified that stroke and PRES are not otherwise mutually exclusive. (Tr. 290.) Dr. Huq likewise opined that A.J.K.'s PRES could have resulted in stroke. (Tr. 86.) Accordingly, even if it is reasonable to invoke stroke, the expert discussion casts doubt on the idea of stroke having occurred to the exclusion of PRES.

In light of all of the above, while no conclusive diagnosis can be rendered, Dr. Huq is persuasive in contending that A.J.K. can reasonably be diagnosed with PRES.

v. There is no evidence of post-vaccination inflammation

Importantly, the diagnosis of PRES does not in itself identify a cause. PRES is a syndrome that is still not considered to be well known and it is usually a diagnosis of exclusion. "Given the heterogeneity of underlying disease conditions and toxic triggers, it is very likely that – at least in the initial phase of the disease – different pathophysiological mechanisms and combinations therefor play a role. However, studies investigating pathophysiological subgroups in PRES are lacking." (Liman et al., *supra* Ex. C, Tab 4, p. 27.) Absent additional clinical clues, A.J.K.'s condition is still best viewed as effectively idiopathic even though petitioners have substantiated that PRES is an appropriate diagnosis. Thus, the most challenging point for petitioners under *Althen* prong two is the question of what, if any, clinical evidence is available to demonstrate that the theorized cytokine response to vaccination is, in fact, implicated as a cause of A.J.K.'s own condition.

Measurement of cytokines is simply not something that occurs in any real-world clinical context. Respondent's experts indicate that fever, elevated CRP, and abnormal CSF results, are important proxies for the type of cytokine driven inflammation petitioners posit. However, A.J.K.'s case was negative for these findings.[43] (Tr. 294, 323, 336; Ex. C, p. 8.) Dr. Gershwin counters that he has not proposed that any "burst" of systemic cytokine activity occurred. (Tr. 211.) Thus, he specifically disagrees that either fever, elevated CRP, or abnormal CSF, need to be present for his theory to be operative. (Tr. 405-06.) However, even if fever or elevated CRP are not strictly necessary for Dr. Gershwin's theory to apply, the absence of these findings still leaves a paucity of supporting clinical evidence. As Dr. Bingham noted during the hearing, petitioners' explanation of events "may have its own logic, but it isn't evidenced." (Tr. 294.) Absent clinical evidence of inflammation, A.J.K.'s acute neurologic event ultimately remains enigmatic regardless of whether it is diagnosed as PRES. Thus, even accepting petitioners' contention that A.J.K. did suffer PRES, they have not preponderantly demonstrated any logical sequence of cause and effect implicating A.J.K.'s vaccinations as a cause of her PRES.[44]

[43] A.J.K. did have a slight fever as of her second emergency department presentation, but not during her initial presentation. Thus, Dr. Gershwin disclaimed reliance on the presence of fever. (Tr. 404-05.)

[44] Despite the lack of evidence of inflammation, petitioners' experts in effect argue that the PRES itself is the evidence of a cytokine response given the context of this case. (Tr. 261-64.) In many settings, this type of opinion has been dismissed as circular logic. *See, e.g.*, *Dodd v. Sec'y of Health & Human Servs*., No. 09-0585V, 2013 WL 3233210, at *14 (Fed. Cl. Spec. Mstr. June 5, 2023) (explaining that "Dr. Kinsbourne's circular logic, that one event was caused by another simply because the second event occurred, is also unavailing"), *review denied*, 114 Fed. Cl. 43 (2013); *Morgan v. Sec'y of Health & Human Servs*., No. 12-77V, 2017 WL 6893079, at *22 (Fed. Cl. Spec. Mstr. Dec. 6, 2017) (concluding that "Petitioner's experts *assumed* that the very fact she experienced a rare injury at all was circumstantial proof of her 'unique genetic repertoire.' This kind of circular logic (the injury itself is proof of causation) does not meet the preponderant evidentiary standard set for a vaccine injury claim." (internal citation omitted)). However, had petitioners met their burden of proof under *Althen* prong one, this idea *might* have warranted further exploration given that the diagnostic dispute between the parties does encompass a key pathogenic distinction. *Accord Stone v. Sec'y of Health & Human Servs*., 676 F.3d 1373, 1382-83 (Fed. Cir. 2012) (rejecting the argument that the fact that an expert "reasoned backwards" from the fact of the injury to the conclusion that the injury was caused by a genetic mutation necessarily constituted

VII. Conclusion

Petitioners have my deepest sympathy for what they and A.J.K. have suffered. There is no question that A.J.K. suffered as a devastating and profound injury the consequence of which they are still navigating. The outcome of the causal analysis in this case in no way minimizes any of that. Moreover, given the timing of A.J.K.'s acute neurologic event, I understand why petitioners themselves suspect the vaccinations to have been a factor. However, even accepting their preferred diagnosis of PRES, there is not preponderant evidence that vaccinations can be a substantial contributing factor leading to PRES generally or any significant clinical evidence supporting a logical sequence of cause and effect implicating the vaccines as a cause of A.J.K.'s own PRES specifically. Thus, for all the reasons described above, I find that petitioners are not entitled to compensation and this case is dismissed.[45]

IT IS SO ORDERED.

s/Daniel T. Horner
Daniel T. Horner
Special Master

"circular logic" where that reasoning was based on a number of factors that cumulatively supported the conclusion); *Capizzano v. Sec'y of Health & Human Servs*., 440 F.3d 1317, 1326-27 (Fed. Cir. 2006) (cautioning that the second *Althen* prong is "not without meaning," but also explaining that "if close temporal proximity, combined with the finding that the hepatitis B vaccine can cause RA, demonstrates that it is logical to conclude that the vaccine was the cause of the RA (the effect), then medical opinions to this effect are quite probative").

[45] In the absence of a timely-filed motion for review of this Decision, the Clerk of the Court shall enter judgment accordingly.